BRITISH MEDICAL JOURNAL

LONDON SATURDAY APRIL 25 1959

THE HEREDITARY HAEMORRHAGIC DISEASES: THEIR CLASSIFICATION AND DIAGNOSIS*

BY

ARMAND J. QUICK, M.D., Ph.D.

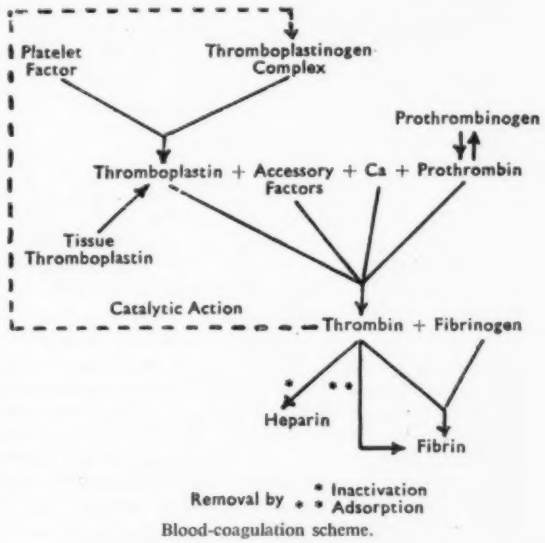
From the Department of Biochemistry, Marquette University School of Medicine, Milwaukee, Wisconsin

We in America take great pride in William Beaumont's outstanding contribution to scientific medicine. He, an Army surgeon—untrained in research and stationed in a frontier wilderness—advanced knowledge concerning gastric physiology more than any other individual before him because he had the unique opportunity to look directly into the human stomach. The advantage of exploring the machinery of the body by visual means is easily comprehended, but its limitations become evident when one attempts to look into the body to learn, for example, how blood accomplishes its haemostatic function. For this purpose a physical instrument comparable to the bronchoscope would be valueless. A more subtle approach with what might be described as physiological haematoscopes is far more promising. These hypothetical instruments are the blood-clotting tests, most of which have been developed only during the past two and a half decades. These alone would hardly suffice were it not for the fortuitous existence of at least twelve or more hereditary haemorrhagic diseases in each of which there is usually only one particular factor of the haemostatic mechanism that is defective.

Much can be learned concerning the probable mechanism of haemostasis by correlating the data that have been obtained recently from the study of the hereditary haemorrhagic diseases by means of the modern laboratory methods. It is the objective of this presentation not merely to present a classification of these diseases and to discuss their diagnosis, but also to utilize some of the salient observations made on the coagulation defects of the various bleeding conditions to formulate a more critical concept of the stanching process.

In the clotting of blood an undetermined number of co-ordinated reactions occur between factors from the plasma and platelets; two recognizable end-products are formed—namely, thrombin and fibrin. For convenience the process can be divided into three major steps. The first consists in the generation of thromboplastin from the interaction of a platelet factor and several agents of the plasma. Of the latter, thromboplastinogen (antihaemophilic globulin or factor VIII) and P.T.C. (plasma thromboplastin component, Christmas disease, or factor IX) are the two which have been most clearly established. The second step is the conversion of prothrombin to thrombin by the action of thromboplastin and several plasma agents such as labile factor (ac-globulin, proaccelerin, or factor V), stable factor (proconvertin or factor VII), and perhaps other agents like the Stuart-Prower factor. The third step is the formation of fibrin by the action of thrombin on fibrinogen.

For ease and clarity of presentation, the clotting mechanism may be summarized in the form of a relatively simple scheme (see Diagram). It will be observed that thrombin has two important functions: it converts fibrinogen to fibrin and it catalyses in some manner the production of intrinsic thromboplastin. The control of this autocatalysis appears to reside in the fibrin reticulum, which has a great affinity for thrombin, and therefore removes it promptly from the reaction



Blood-coagulation scheme.

mixture. Particularly noteworthy is the existence of two types of thromboplastin. One is widely distributed in the various tissues of the body in a preformed state but is absent in the blood. The other is formed from the interaction of platelets and several plasma constituents. Whether or not tissue thromboplastin has a primary function in haemostasis is unknown, and knowledge concerning its relationship to intrinsic or

*This paper was presented as a Special University Lecture in Pathology at the University of London, on October 6, 1958. A more descriptive title would have been "The Haemorrhagic Diseases as Means to Study Haemostasis." The experimental work was supported by a grant (H1612C12) from the National Heart Institute, National Institutes of Health, United States Public Health Service.

plasma thromboplastin has not advanced beyond the stage of speculation. Since even a severe haemophiliac has a normal concentration of thromboplastin in his tissues, it seems likely that it may be only the intrinsic thromboplastin which is primarily concerned with haemostasis.

Classification of the Hereditary Haemorrhagic Diseases

The hereditary haemorrhagic diseases fall into three classes (Table I). In the first, the defect is entirely in the clotting reaction. The term "haematostaxis" is proposed for this group. In the second class, a vascular dysfunction in addition to a coagulation defect is present. A suitable name for this class is haematostaxis with angiostaxis; the latter term was first proposed by Lethaby Tidy (1926). In only one known bleeding disease—namely, telangiectasia—is there evidence that the defect is solely in the vascular structure.

TABLE I.—*Classification of the Hereditary Haemorrhagic Diseases*

	Key Diagnostic Tests	Type of Heredity
I. Due to Clotting Dysfunction (Haematostaxis):		
A. Hypoprothrombinaemic states:		
a. Hypoprothrombinaemia vera, Type I	Prothrombin time	Autosomal, recessive
b. Hypoprothrombinaemia, Type II	,, ,,	Autosomal, dominant
c. Labile factor deficiency ..	,, ,,	Autosomal, recessive
d. Stable factor deficiency ..	,, ,,	,, ,,
B. Hypothromboplastinaemias:		
a. Haemophilia vera	Prothrombin consumption time, and thromboplastin generation test	Sex-linked recessive
b. Haemophilia B (P.T.C. deficiency, Christmas disease)	,, ,, ,,	,, ,,
C. Combined hypoprothrombinaemic states and hypothromboplastinaemias (Stuart-Prower factor deficiency)	Prothrombin time and prothrombin consumption time	Autosomal, recessive
D. Hyperheparinaemia	Thrombin time	,, ,,
E. Hypofibrinogenaemia	Clotting time and fibrinogen determinations	,, ,,
II. Due to Clotting Defect Combined with Vascular Dysfunction (Haematostaxis and Angiostaxis):		
A. Pseudohaemophilia A (von Willebrand's disease)	Bleeding time	Autosomal, dominant
B. Pseudohaemophilia B	Bleeding time and prothrombin consumption time	Autosomal, recessive
C. Thrombasthenia	Bleeding time, platelet count, and prothrombin consumption time	Autosomal, dominant
III. Due to Vascular Abnormality (Angiostaxis):		
A. Telangiectasia	Detection of spider naevi	,, ,,

Only a few key diagnostic tests are needed to characterize and diagnose most of the bleeding diseases. The prothrombin time and the prothrombin consumption time have the widest application, but the thromboplastin generation test is particularly valuable for studying the haemophilic group. In addition to the laboratory tests, information supplied by the clinical picture and by the hereditary pattern may often be very helpful in the differential diagnosis.

The Hypoprothrombinaemic States

Since the one-stage prothrombin time was developed on the basis of the classical theory of coagulation, it was natural to assume that the test determined prothrombin specifically. I became one of the staunch defenders of this view; yet, paradoxically, I was the first to cast doubt unwittingly on the correctness of this assumption when I discovered that the prolonged prothrombin time of stored plasma and of plasma from a dicoumarolized subject, when mixed, mutually corrected each other (Quick, 1943). Somewhat later, Owren (1947) found a patient who lacked the factor that disappears in stored normal plasma. From the studies of Mann *et al.* (1947), MacMillan (1948), and particularly Alexander *et al.* (1949), a third factor was established which has been given various names: co-thromboplastin, S.P.C.A., proconvertin, factor VII, and stable factor. Alexander *et al.* (1951) were the first to report a bleeding case due to a deficiency of this clotting agent. During this development I had the good fortune to find a true hypoprothrombinaemic state in two brothers (Quick, 1947). Thus it became obvious that three types of bleeding diseases exist which are hereditary and have in common a markedly prolonged prothrombin time.

A comparison of the three states can best be made by selecting a representative case of each. A girl now 8 years old who has a deficiency of prothrombin and a second girl who is 7 years old serve as typical cases of the first two states. For labile factor deficiency I have chosen the patient (aged 27) who was reported by Brink and Kingsley (1952). In Table II the important laboratory findings are given. The differential diagnosis is simple. Serum rich in stable factor corrects only plasma deficient in this agent. Rabbit plasma, which has an exceedingly high concentration of labile factor when treated with an adsorbent such as $Ca_3(PO_4)_2$ or $BaSO_4$ to remove prothrombin and stable factor, becomes a diagnostic reagent which corrects only plasma lacking labile factor. True hypoprothrombinaemia is corrected by neither reagent nor by a mixture of the two.

On inspecting the data of Table II, the finding which stands as if it were in bold relief is the normal clotting time in both labile and stable factor deficiencies, in contrast to the markedly prolonged value in true hypoprothrombinaemia. Terms such as accelerators and convertins have been used rather loosely, and many investigators maintain that both labile factor and stable factor act as accelerators. Oddly, in the two conditions in which they are lacking the clotting time is normal; whereas in true hypoprothrombinaemia, in which both are normal in concentration, the clotting time is very prolonged. Since the three patients selected may be regarded as severe bleeders, the unreliability of the clotting time as a measure of haemostasis is clearly brought out.

TABLE II.—*Laboratory Findings in the Hypoprothrombinaemic States*

	Deficiency of			Normal
	Prothrombin	Stable Factor	Labile Factor (Brink–Kingsley)	
Prothrombin time:				
Basic (seconds)	73	60	41½	12
With added S.F.* (seconds) ..	60	13	—	12
,, ,, L.F.† ,, ..	51	60	10½	12
Clotting time (minutes)	60+	7	7	5–10

* Stable factor = aged normal serum. † Labile factor = deprothrombinized rabbit plasma. Data were obtained from case histories.

The true significance of the prothrombin time is still poorly understood, as shown by the following observations. The girl who lacks prothrombin and also the one who is deficient in stable factor were suffering from severe intramuscular haemorrhages at

the time when each received 250 ml. of fresh frozen plasma. In the first patient the prothrombin time dropped from 73 to 19 seconds, and in the second from 60 to 22 seconds. In both, the haemorrhages were promptly arrested, and the absorption of blood began after 24 hours. In the first girl the beneficial effect lasted five weeks, even though the prothrombin time was already increased within 24 hours after the transfusion. In the second a transfusion was again required in two weeks. It seems likely that the prothrombin time in these instances did not accurately measure the haemorrhagic state. In the first girl the spontaneous haemorrhage was controlled at a prothrombin time level of 19 seconds, yet in two other subjects who also have true hypoprothrombinaemia (Quick, 1947) bleeding often occurs from trauma at this level.

To explain this apparent paradox it may perhaps be necessary to distinguish between spontaneous and traumatic bleeding. Such an idea has recently been expressed by Jacobson (1958): "Other factors than trauma or the penetration of vessels must be the cause of spontaneous bleeding. These factors must arise from a systemic disorder which, in my opinion, lies somewhere in the endocrine balance. The problem of hemostasis in spontaneous bleeding has been either ignored or neglected or managed as if it were traumatic hemorrhage. The literature makes no distinction between the two and thus the fallacies of this approach have been perpetuated." The prompt clinical response of both girls to the transfusions suggests that the plasma supplied something that their organism needed for vascular integrity and normal function, which includes the reabsorption of extravasated blood. Whether this factor is supplied directly by the plasma or is the resultant of precursors such as prothrombin and stable factor is entirely speculative.

It may be significant that various clotting factors have a relatively high metabolic turnover. When, for instance, thromboplastinogen is supplied by means of a fresh plasma transfusion to a severe haemophiliac, its disappearance from the blood stream is fairly rapid. Likewise, when the subject whose prothrombin activity is depressed by dicoumarol is given a transfusion of normal plasma the resulting elevation is of short duration and little remains after 24 hours. It is not known why certain clotting factors seem to be consumed metabolically at a rapid rate. There may be a possibility that this is in some manner related to the maintenance of the normal function of the blood vessel and the prevention of spontaneous haemorrhages. The widely held concept that the clotting mechanism is kept in readiness to bring about stanching immediately after a blood vessel is injured may not be sufficiently inclusive.

The hereditary pattern of the known types of hypoprothrombinaemic states are alike. All are transmitted as non-sex-linked or autosomal, recessive traits. Since a bleeder can result only if both parents carry the defective gene (and, even then, only one out of four should theoretically inherit both defective genes and be a bleeder), it is understandable why these hypoprothrombinaemic states are rare.

The Haemophilias

One of the more interesting developments in the study of hereditary haemorrhagic diseases was the discovery that two distinct types of haemophilia exist. The thromboplastin generation test developed by Biggs and Douglas (1953) played an important part in establishing the existence of the second type of haemophilia and in its differentiation from the classical type (Biggs *et al.*, 1952). Interestingly, these two are the only bleeding diseases known to be transmitted as sex-linked recessives. Both follow the rule that the degree of the severity of the defect remains constant from generation to generation. Interestingly, the famous bleeding disease of Tenna, Switzerland, is mild haemophilia B or Christmas disease. The two descendants of this family whom I have studied have only a slightly prolonged clotting time and a relatively mild clinical bleeding state. It is likely that all the affected members of this pedigree have been mild bleeders, which would explain why many lived beyond the adolescent period despite lack of adequate medical care.

In regard to a name for the new type of haemophilia, I prefer the term "haemophilia B," in agreement with the French and Swiss workers, because the two diseases are clinically very similar and both have the characteristic hereditary pattern. The observation, made first by Biggs *et al.* (1952), that the ratio of classical haemophilia to the new type is roughly 5 or 4 to 1, appears to hold throughout the whole population of the world. Whether the reason for this is a different rate of mutation presents a provocative genetic problem.

While the thromboplastin generation test has been invaluable in establishing haemophilia B as a distinct clinical entity, the prothrombin consumption test, especially the modification in which an extract of erythrocytes is used, has proved to be an important tool for obtaining further information concerning the basic defect. In Table III the application of the prothrombin consumption test to true haemophilic and haemophilia B blood is shown. Native plasma from which the platelets are removed is the test medium. When platelet-poor plasma is clotted, almost no prothrombin is consumed; consequently, the prothrombin time of the resulting serum is short. The addition of aged serum to the plasma does not improve the prothrombin consumption, as is to be expected, since serum lacks the platelet factor. The addition of haemolysate, which has platelet activity, causes a high consumption of prothrombin in normal plasma, but not in either type of haemophilia. The addition of both haemolysate and serum to haemophilia B plasma brings about a very high utilization of prothrombin, but not when added to true haemophilic plasma. When, however, haemolysate and fresh normal plasma are added to true haemophilic plasma a striking consumption of prothrombin occurs;

TABLE III.—*Differentiation of Haemophilia B from True Haemophilia by the Prothrombin Consumption Test, Using Haemolysate, Normal Aged Serum, and Plasma*

	ml.	Prothrombin Consumption Time		
		Normal (sec.)	True Haemophilia (sec.)	Haemophilia B (sec.)
Native platelet-poor plasma ..	1·0	8	8	11
With: Haemolysate	0·1	55	8	11
Serum, aged normal ..	0·03	8½	8	11
Haemolysate	0·1	135	8	70
Serum	0·03			
Haemolysate	0·1	55	30	11*
Fresh normal plasma ..	0·005			

* Even 0·1 ml. of plasma did not increase the prothrombin consumption.

but on adding it to haemophilia B plasma no significant conversion of prothrombin is effected.

The results recorded in Table III are in accord with the studies of other investigators, showing that the production of intrinsic thromboplastin requires at least three factors: a phospholipid, thromboplastinogen, and P.T.C. or Christmas factor. While it appears certain that the first is supplied by platelets, erythrocytin (the factor isolated from erythrocytes) may actually be the immediate reagent that reacts with the plasma components, since it is much more active than platelet extract. It is interesting to speculate whether the platelet factor is converted to erythrocytin before it brings about the production of thromboplastin. The factor lacking in haemophilia B does not appear to be in the active state in fresh plasma but is present abundantly in normal serum, suggesting that it becomes activated during coagulation. Nothing is known of how this activation is effected. The possibility is presented that a condition may perhaps occur in which lack of activation rather than a true deficiency of Christmas factor is the basic defect.

The Haematostaxic-Angiostaxic Group

Attention should be called to the group of hereditary haemorrhagic diseases in which the bleeding time is prolonged. A discussion of these conditions is beyond the scope of this paper, but a few comments should be made. In the past these diseases were all grouped under the general class of thrombopathies, implying that the defect was specifically in the platelets. While it is well established that a prolonged bleeding time is found in severe thrombocytopenia and also when the platelets are qualitatively defective, it is now recognized that the bleeding time may be abnormally long in conditions in which the platelets are quantitatively and qualitatively normal but the plasma lacks a factor which is identical or at least very similar to the agent that is lacking in true haemophilia. The latter diseases are hereditary but not sex-linked and therefore occur in both males and females. Apparently a normal bleeding time requires both a platelet and plasma factor.

Hyperheparinaemia

Particularly devastating to my own rather smug concept of haemostasis have been the observations made on a young woman with pronounced hyperheparinaemia which is probably of congenital origin (Quick and Hussey, 1957). Though her clotting time is usually 40 minutes or more, and at times infinity, her bleeding tendency is surprisingly mild. Only after surgical operations and after the birth of her two babies has she encountered real difficulties. In fact, she had to have over 30 transfusions to control the bleeding after each of her two deliveries. Even when her blood is incoagulable she does not bruise easily, has no epistaxis, no haemarthroses, no deep intramuscular bleeding, no haematuria or any other type of haemorrhage. Since her blood does not clot in a glass test-tube at 37° C., it seems unlikely that intracorporeal clotting could take place. Any amount of thrombin that could be conceivably formed would be promptly neutralized by the excess of heparin in her blood.

The bleeding state caused by hyperheparinaemia is especially interesting in that heparin probably does not have a physiological role in coagulation. It is likely that the hypocoagulable state is only incidental. In preparing this patient for dental surgery, the hyperheparinaemia was reduced significantly with cortisone and fresh frozen plasma transfusions. No abnormal bleeding occurred, but the hyperheparinaemia again increased immediately after treatment was stopped. In this patient the difference between the control of spontaneous and traumatic haemorrhage is clearly illustrated.

Conclusions

Even from this rather cursory consideration of a few of the hereditary haemorrhagic diseases, it becomes clear that the commonly held concepts of haemostasis need re-evaluation. The view that the fibrin clot serves as a mechanical seal and that the speed with which it is formed is significant in haemostasis is not only unsound but is also hampering progress. Perhaps too much attention is being given to so-called accelerators and inhibitors. While it is still largely pure speculation, one must not overlook the possibility that the first stages of haemostasis are carried out by the vessel itself. Even in severe hyperheparinaemia when the formation of thrombin is almost completely suppressed, haemostasis is remarkably effective and breaks down only when the injury is very severe. The generation of thrombin and the formation of a fibrin clot may perhaps function only as third-line measures of defence against excessive loss of blood. It is not improbable that some of the recognized clotting factors may have as their primary function the maintenance of the integrity of the vessel and its normal physiological function. Thus, in acute thrombocytopenic purpura the bleeding is essentially angiostaxic in type. The clotting time in this disease is never prolonged and often is shorter than normal.

The development of the newer clotting tests has made it possible to diagnose and classify satisfactorily the hereditary haemorrhagic diseases. Their treatment, however, has not reached such a successful stage, because the mechanism of haemostasis is still imperfectly understood. To obtain the required information to solve the enigma of stanching, the haemorrhagic diseases themselves may serve as the most promising source. When sufficient data have been gathered it may perhaps be necessary to revise drastically our present concepts. It may be well to remember the classical advice of Descartes: "Pour atteindre la verité, il faut, une fois dans sa vie, se dèfaire de toutes les opinions qu'on a reçues et reconstruire de nouveau et dès le fondement, tout le système de sès connaissances."

REFERENCES

Alexander, B., de Vries, A., Goldstein, R., and Landwehr, G. (1949). *Science*, **109**, 545.

—— Goldstein, R., Landwehr, G., and Cook, C. D. (1951). *J. clin. Invest.* **30**, 596.

Biggs, R., and Douglas, A. S. (1953). *J. clin. Path.*, **6**, 23.

—— —— Macfarlane, R. G., Dacie, J. V., Pitney, W. R., Merskey, C., and O'Brien, J. R. (1952). *Brit. med. J.*, **2**, 1378.

Brink, A. J., and Kingsley, C. S. (1952). *Quart. J. Med.*, **21**, 19.

Jacobson, P. (1958). *Virginia med. Monthly*, **85**, 548.

MacMillan, R. L. (1948). *Science*, **108**, 416.

Mann, F. D., Hurn, M., and Magath, T. B. (1947). *Proc. Soc. Exp. Biol. (N.Y.)*, **66**, 33.

Owren, P. A. (1947). *Lancet*, **1**, 446.

Quick, A. J. (1943). *Amer. J. Physiol.*, **140**, 212.

—— (1947). *Lancet*, **2**, 379.

—— and Hussey, C. V. (1957). *Amer. J. med. Sci.*, **234**, 251.

Tidy, H. L. (1926). *Lancet*, **2**, 365.

ADULT LEUKAEMIA

TRENDS IN MORTALITY IN RELATION TO AETIOLOGY

BY

W. M. COURT BROWN, M.B., B.Sc., F.F.R.

Director of the Medical Research Council's Group for Research on the General Effects of Radiation, Western General Hospital, Edinburgh

AND

R. DOLL, M.D., D.Sc., F.R.C.P.

Deputy Director of the Medical Research Council's Statistical Research Unit, London School of Hygiene and Tropical Medicine

Variations in the mortality attributed to leukaemia throughout the world have been reviewed by the World Health Organization (1955) and by Clemmesen and Sørensen (1958). For all countries for which figures are available, the data agree in showing that: (1) the crude death rate has increased steadily over the past 30 to 40 years; (2) the male death rate has invariably been greater than the female rate, though never as much as twice as great; and (3) the death rate after being relatively high in the first five years of life falls to a minimum between the ages of 20 and 34 years and then rises again at age 35 years and above; in all countries but Japan the peak mortality in old age has been substantially higher than the peak in childhood.

There are, however, considerable differences between countries in the level of the death rate. Thus the crude rates have been highest in Denmark and the U.S.A. and lowest in Eire and Japan; in 1950–2, for example, the Danish rate for males was 73 per million, the rate in the U.S.A. was 71 per million, and those in Eire and Japan 35 and 20 per million respectively. The rate in England and Wales was intermediate at 49 per million. The differences are not due to variations in the age distributions of the populations, since the differences between death rates standardized for age are even greater (Registrar-General, 1958).

Since 1950 some countries have classified leukaemia deaths into several categories, according to the recommendations made in the *International List of Causes of Death* (Sixth Revision). The Registrar-General (1958) has reviewed the data for England and Wales and published separate data for the mortality by sex and age and for the trend in mortality with time for (*a*) lymphatic leukaemia, (*b*) myeloid leukaemia, (*c*) monocytic leukaemia, and (*d*) acute leukaemia of unspecified type. These data show substantial differences between the different types. The most striking is that the age distribution in both lymphatic and acute unspecified leukaemia is bimodal, with sharp maxima in early childhood and in old age, whereas the rates for myeloid and monocytic leukaemia increase slowly with age and at no period fall much below the level recorded for the first five years of life. In contrast the trend in mortality since 1950 is similar for all types. At the age of 15 years and above, the mortality of each type has increased, whereas below this age it has remained stationary.

The classification used in the *International List* failed, however, to distinguish between the acute and the chronic forms of the disease; this is unsatisfactory, as there is reason to suppose that some of the factors concerned in the causation of the two clinical types may be different.* There is, for example, no evidence to implicate ionizing radiations as a cause of chronic lymphatic leukaemia, although they may cause acute leukaemia and, perhaps to a less extent, chronic myeloid leukaemia. The distinction between chronic lymphatic, chronic myeloid, and acute leukaemia can, moreover, be made by cytological examination with some confidence, whereas the distinction between the various types of acute leukaemia is less certain and differences of opinion about the correct cytological classification of individual cases are common. Hospital data suggest that the proportion of acute cases diminishes steadily with age, that the mortality from both types of chronic leukaemia rises progressively from childhood, and that the bimodal form of the age distribution is confined to the acute cases (MacMahon and Clark, 1956).

It was thought, therefore, that information of interest might be obtained if the national data could be recast to show trends in mortality for (*a*) chronic lymphatic leukaemia, (*b*) chronic myeloid leukaemia, and (*c*) all forms of acute leukaemia grouped together. An opportunity to do this was provided by the Registrar-General of England and Wales when he extracted information from the records of all persons certified as dying from leukaemia between 1945 and 1957 and made it available to the Medical Research Council for the purposes of another investigation. It has been possible to use this information to reclassify the cases and to calculate separate mortality rates for the acute and chronic forms of the disease. The present paper relates to the data that have been obtained for adults aged 15 years and above. The trends in mortality in childhood have been discussed in detail elsewhere (Hewitt, 1955; Burnet, 1958).

Results

Full information about the clinical and cytological types of the disease is not provided with all death entries; the cases were therefore initially classified into the following nine groups: (1) acute lymphatic leukaemia; (2) chronic lymphatic leukaemia; (3) lymphatic leukaemia of unspecified clinical type; (4) acute myeloid leukaemia; (5) chronic myeloid leukaemia; (6) myeloid leukaemia of unspecified clinical type; (7) acute leukaemia of other and unspecified cytological types, including monocytic leukaemia and erythroleukaemia; (8) chronic leukaemia of unspecified cytological type; and (9) leukaemia not otherwise described.

Deaths attributed to plasma-cell leukaemia have been excluded, as it was thought that they ought to be classified with multiple myeloma.

Male death rates from each of these categories of leukaemia are shown in Tables I, II, and III for the three periods 1945–9, 1950–4, and 1955–7. In each period the rates are shown separately for five-year age groups from 15–19 years to 80 years and over. Since 1950 the Registrar-General has inquired about the cytological type whenever this has been omitted from the initial certificate, and it will be seen that the proportion of deaths attributed to "leukaemia," without further specification, has fallen substantially. The proportion of deaths attributed to lymphatic leukaemia or to myeloid leukaemia, in which the description of

*The classification has been modified in the seventh revision of the List and has been used by the Registrar-General of England and Wales for all leukaemic deaths occurring since the end of 1957.

TABLE I.—*Male Death Rate from Leukaemia per Million Living, England and Wales, 1945–9; Subdivided by Age and by Type of Leukaemia*

Age (Years)	Acute Lymphatic	Chronic Lymphatic	Unspecified Lymphatic	Acute Myeloid	Chronic Myeloid	Unspecified Myeloid	Other and Unspecified Acute Leukaemia	Unspecified Chronic Leukaemia	Unspecified Leukaemia	Total Leukaemia
15–	5·97	0·27	2·44	5·70	0·41	1·36	5·15	0·13	2·58	24·01
20–	2·65	0·25	1·39	2·65	0·88	2·39	5·03	0·25	1·26	16·75
25–	1·93	0·12	1·33	3·26	1·33	1·69	3·64	0·00	0·97	14·27
30–	1·74	0·37	2·24	5·97	1·99	3·98	3·97	0·13	1·61	22·00
35–	1·63	0·93	1·17	4·20	1·86	5·60	3·97	0·00	2·33	21·69
40–	1·59	1·22	2·44	4·88	2·56	5·49	6·96	0·12	1·22	26·48
45–	2·54	1·83	6·21	5·93	3·67	6·07	7·62	0·28	3·53	37·68
50–	3·98	4·15	7·47	4·65	3·65	8·30	8·31	0·17	5·48	46·16
55–	3·15	7·78	14·83	6·86	3·15	9·64	8·15	0·55	7·97	62·08
60–	5·34	12·59	21·56	6·62	5·34	14·30	8·32	1·07	12·38	87·52
65–	4·62	16·69	21·06	7·70	13·10	15·15	8·22	0·52	11·81	98·87
70–	6·56	15·88	29·71	4·49	8·98	14·85	8·98	1·38	12·78	103·61
75–	7·59	17·52	28·62	3·50	8·76	18·11	6·43	1·75	9·93	102·21
80+	4·73	13·24	11·35	2·84	1·89	8·51	4·73	0·00	8·51	55·80
All ages 15 yrs. +	3·22	3·94	7·25	4·98	3·18	6·43	6·06	0·31	4·29	39·66

TABLE II.—*Male Death Rate from Leukaemia per Million Living, England and Wales, 1950–4; Subdivided by Age and by Type of Leukaemia*

Age (Years)	Acute Lymphatic	Chronic Lymphatic	Unspecified Lymphatic	Acute Myeloid	Chronic Myeloid	Unspecified Myeloid	Other and Unspecified Acute Leukaemia	Unspecified Chronic Leukaemia	Unspecified Leukaemia	Total Leukaemia
15–	7·02	0·00	2·39	9·26	0·30	2·39	4·92	0·00	0·75	27·03
20–	4·72	0·29	2·57	5·86	1·00	2·43	4·29	0·00	0·00	21·16
25–	3·17	0·13	1·40	6·60	1·78	2·92	4·45	0·00	0·38	20·83
30–	2·62	0·50	1·12	5·49	2·49	2·74	3·86	0·00	0·37	19·19
35–	3·08	0·77	1·54	7·70	3·33	4·62	6·03	0·26	0·64	27·97
40–	3·00	1·08	2·04	8·75	3·83	5·88	6·84	0·00	0·84	32·26
45–	3·78	3·27	5·05	9·71	5·05	7·32	8·08	0·00	1·14	43·40
50–	4·39	6·29	8·05	9·66	5·56	8·78	6·28	0·00	1·90	50·91
55–	5·55	12·72	14·87	11·11	7·52	13·26	9·68	0·54	3·58	78·83
60–	7·75	20·33	21·37	14·04	11·11	18·86	14·04	0·21	4·19	111·90
65–	8·43	31·68	31·68	17·88	15·84	24·78	17·63	0·26	5·62	153·80
70–	7·78	33·15	35·52	15·56	19·96	27·74	12·18	0·68	5·41	157·98
75–	10·58	44·44	38·62	12·70	20·11	26·46	13·23	1·58	8·47	176·19
80+	3·30	36·30	34·65	18·15	9·90	23·93	10·73	2·47	2·48	141·91
All ages 15 yrs. +	4·74	7·54	8·75	9·48	5·51	8·70	7·47	0·19	1·63	54·01

TABLE III.—*Male Death Rate from Leukaemia per Million Living, England and Wales, 1955–7; Subdivided by Age and by Type of Leukaemia*

Age (Years)	Acute Lymphatic	Chronic Lymphatic	Unspecified Lymphatic	Acute Myeloid	Chronic Myeloid	Unspecified Myeloid	Other and Unspecified Acute Leukaemia	Unspecified Chronic Leukaemia	Unspecified Leukaemia	Total Leukaemia
15–	7·56	0·41	1·22	8·78	0·24	2·20	8·55	0·00	0·49	29·45
20–	6·10	0·00	0·99	7·80	1·46	1·95	5·87	0·00	0·73	24·90
25–	2·92	0·67	0·67	6·52	2·47	2·92	5·18	0·00	0·22	21·57
30–	3·32	0·21	1·24	7·26	2·28	2·69	5·80	0·00	0·42	23·22
35–	2·41	0·88	1·76	9·45	5·71	2·85	5·51	0·00	0·44	29·01
40–	3·33	3·12	1·67	10·81	3·74	6·86	7·28	0·00	0·21	37·02
45–	3·94	4·51	3·69	12·09	5·54	6·15	6·77	0·00	1·23	45·92
50–	4·21	6·21	4·88	13·75	8·20	7·76	8·65	0·22	1·11	54·99
55–	5·71	14·69	9·53	19·31	8·43	11·98	12·80	0·00	1·09	83·54
60–	9·57	25·64	16·61	19·14	17·09	19·49	18·47	0·34	2·74	129·09
65–	10·54	35·44	31·65	24·47	17·29	22·37	16·04	0·42	5·91	164·13
70–	11·74	48·65	40·27	36·91	26·84	33·00	25·73	0·57	7·27	230·98
75–	13·81	69·07	47·29	35·39	39·64	33·68	28·52	1·73	6·04	275·17
80+	10·95	83·04	54·95	21·94	40·29	25·64	25·72	2·46	8·53	273·52
All ages 15 yrs. +	5·72	10·69	8·25	13·44	7·89	8·72	9·83	0·16	1·53	66·23

TABLE IV.—*Estimated Male Death Rates from Chronic Lymphatic Leukaemia, Chronic Myeloid Leukaemia, and Acute Leukaemia, per Million Living, England and Wales, 1945–9, 1950–4, and 1955–7; Subdivided by Age*

Age (Years)	Chronic Lymphatic Leukaemia			Chronic Myeloid Leukaemia			Acute Leukaemia		
	1945–9	1950–4	1955–7	1945–9	1950–4	1955–7	1945–9	1950–4	1955–7
15–	0·5	0·0	0·5	0·6	0·4	0·7	22·9	26·6	28·2
20–	0·5	0·4	0·0	1·8	1·4	1·8	14·5	19·4	23·1
25–	0·2	0·2	0·8	2·0	2·4	3·3	12·1	18·2	17·5
30–	0·9	0·7	0·3	3·3	3·4	3·0	17·8	15·1	20·0
35–	1·5	1·2	1·4	4·0	5·1	6·9	16·2	21·8	20·8
40–	2·4	1·7	3·9	4·8	5·8	5·5	19·3	24·8	27·6
45–	5·0	5·8	6·3	6·8	7·8	7·7	25·9	25·9	32·0
50–	9·1	11·5	9·4	8·4	9·1	11·5	28·7	30·3	34·1
55–	22·5	24·5	21·8	7·3	13·7	12·2	33·3	40·6	49·5
60–	33·2	37·3	38·8	14·0	20·3	27·0	40·3	54·3	63·3
65–	38·0	59·0	62·4	26·0	28·6	27·7	34·9	66·2	74·1
70–	43·2	64·6	84·1	22·1	37·1	42·3	38·4	56·4	104·6
75–	42·8	80·6	112·1	24·7	38·7	59·3	34·7	56·9	103·8
80+	25·5	71·3	137·6	6·2	19·2	39·5	24·1	51·4	76·4
All ages 15 yrs. +	9·1	13·4	16·5	6·5	9·1	11·5	24·0	31·5	38·2

the clinical type is omitted, has also fallen, and it is necessary to take both these changes into account before the trend in mortality for the various types can be assessed. From the Tables it is seen that in each period the ratio of chronic to acute cases increases sharply with age, and it is reasonable to assume that at the younger ages the great majority of cases described as, say, lymphatic leukaemia were really of the acute type, whereas at ages 55 years and over the majority were probably chronic. The most reasonable assumption is that the proportions of acute and chronic cases among those in which the type was not described were, at each age, the same as the proportions among those in which the type was described.

For example, in 1945–9 at ages 15–19 years, the ratio of the death rates attributed to acute and chronic lymphatic leukaemia was 5.97 to 0.27. The death rate attributed to unspecified lympatic leukaemia was 2.44 per million, so that it is assumed that a further $\frac{5.97}{0.27+5.97}\times 2.44$ per million should have been described as acute leukaemia and $\frac{0.27}{0.27+5.97}\times 2.44$ per million as chronic leukaemia. The estimated rates for acute and chronic lymphatic leukaemia then become 5.97+2.33 (i.e., 8.30 per million) and 0.27+0.11 (i.e., 0.38 per million) respectively. Similarly, the estimated rates for acute and chronic myeloid leukaemia become 6.97 and 0.50 per million. Very few deaths were attributed to chronic leukaemia of unspecified cytological type (0.13 per million men in this age group during this period). If it is assumed that they were distributed between chronic lymphatic and chronic myeloid leukaemia in proportion to the estimated death rates for these two conditions, the rate for chronic lymphatic leukaemia becomes $0.38+\frac{0.38}{0.38+0.50}\times 0.13$ (i.e., 0.44) per million and the rate for chronic myeloid leukaemia becomes $0.50+\frac{0.50}{0.38+0.50}\times 0.13$ (i.e., 0.57) per million.

Finally, it is necessary to make some assumption about the true classification of those deaths certified as due to leukaemia without qualification. The rate attributed to this category of leukaemia was 2.58 per million. It has been estimated that, apart from these deaths, the rates attributable to chronic lymphatic, chronic myeloid, and acute leukaemia were 0.44 per million, 0.57 per million, and 20.42 per million (8.30 acute lymphatic, 6.97 acute myeloid, and 5.15 other and unspecified acute leukaemias). If the unspecified deaths were distributed in the same proportions the best estimates of the mortality attributed to the three selected types of leukaemia at ages 15–19 years become 0.50, 0.64, and 22.87 per million respectively. These may be compared with the uncorrected rates, derived from the deaths specifically attributed to these types of leukaemia on the death entries, of 0.27, 0.41, and 16.82 per million. The best estimates of the age-specific male rates for the three selected types of leukaemia in the three periods 1945–9, 1950–4, and 1955–7 are shown in Table IV and the trends in mortality are illustrated in Figs. 1 and 4.

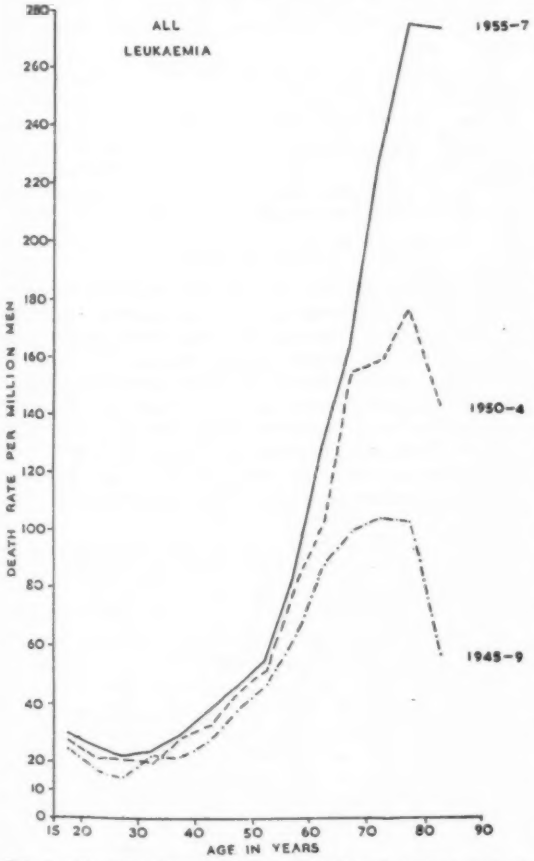


FIG. 1.—Mortality from all forms of leukaemia among men at different ages (from 15 years upwards) in England and Wales in 1945–9, 1950–4, and 1955–7.

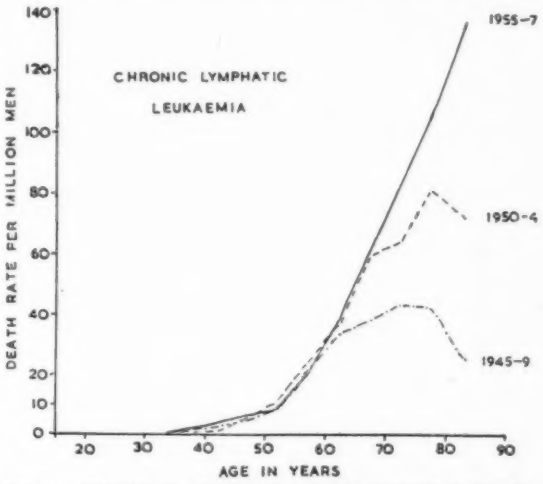


FIG. 2.—Estimated mortality from chronic lymphatic leukaemia among men at different ages (from 15 years upwards) in England and Wales in 1945–9, 1950–4, and 1955–7.

From Fig. 1 it is seen that between 1945–9 and 1955–7 male mortality from leukaemia has increased at all ages. Below the age of 60 years the increase has been of the order of 25%, but at age 70 years and above the rate has more than doubled.

All three types of leukaemia have participated in the increase at the older ages (Table IV and Figs. 2, 3, and 4). At ages under 60 years the increase has been largely confined to acute leukaemia, although there has also been some slight increase in chronic myeloid leukaemia.

The estimated mortality from chronic lymphatic leukaemia at these ages has remained practically constant.

The change in mortality with age differs sharply between the various types of the disease. With chronic lymphatic leukaemia the estimated number of deaths below the age of 30 years is so small that it is not possible to recognize any particular relationship, but above this age the mortality increases rapidly, and in the latest period the increase continues into the oldest age group. In this period, it may be noted that between the ages of 30 and 80 years the estimated mortality increases approximately in proportion to the sixth power of the age. With chronic myeloid leukaemia the estimated mortality increases with age from 15 years upwards, and the mortality increases approximately in proportion to the third power of the age.

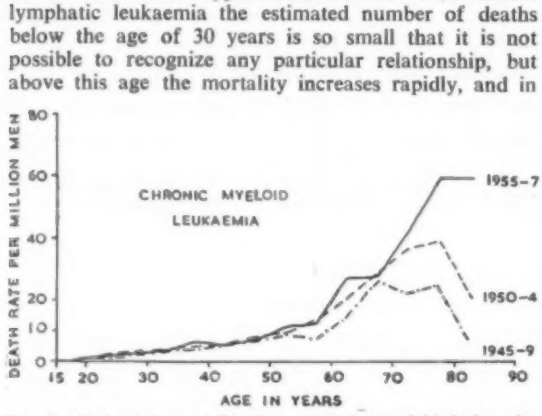


FIG. 3.—Estimated mortality from chronic myeloid leukaemia among men at different ages (from 15 years upwards) in England and Wales in 1945–9, 1950–4, and 1955–7.

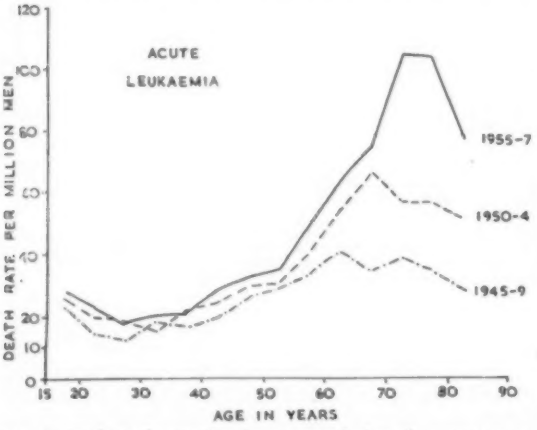


FIG. 4.—Estimated mortality from acute leukaemia among men at different ages (from 15 years upwards) in England and Wales in 1945–9, 1950–4, and 1955–7.

With acute leukaemia the general shape of the curve relating mortality to age is different. The mortality falls from age 15–19 years to a minimum at about 25–29 years and then increases slowly to a maximum at ages 70–74 years. Between the ages of 45 and 74 years, when the rate of increase is greatest, the estimated mortality increases approximately in proportion with the age to the power of 5/2. This rate of increase is slightly slower than that recorded for chronic myeloid leukaemia and is clearly distinguished from the rate of increase observed for chronic lymphatic leukaemia.

Death rates among women have been calculated in the same way as the rates shown for men in Tables I, II, and III. The total female mortality from leukaemia and estimates of the rates attributable to chronic lymphatic, chronic myeloid, and acute leukaemia are shown in Table V for the three periods 1945–9, 1950–4, and 1955–7. The increase in mortality among women has been slightly less than among men during the last few years, so that the sex ratio for all types at all ages has increased from 1.2 to 1 to 1.5 to 1. The trends in mortality with time and the relationships between mortality and age are, however, similar in both sexes. The only exception is that among women there is no evidence of an increase in the mortality attributed to chronic myeloid leukaemia below the age of 60 years.

It is striking that at most ages the sex ratio has a distinctive value for each of the three types of leukaemia studied. In the latest period the crude ratio for chronic lymphatic leukaemia was 2.0 to 1, for chronic myeloid leukaemia it was 1.2 to 1, and for acute leukaemia it was 1.4 to 1. All the ratios have increased since 1945–9, but they have maintained the same hierarchical order.

Sources of Error

It has been possible to calculate separate mortality rates for chronic lymphatic, chronic myeloid, and acute leukaemia only by making the assumption that, at each age and at each of the periods studied, the cases of leukaemia which were incompletely specified were, in fact, distributed among the three types in the same proportions as the cases in which the type was given. If this is not so, the data in Tables IV and V will be inaccurate and the conclusions based on them correspondingly weakened. The proportion of cases

TABLE V.—*Estimated Female Death Rates from Chronic Lymphatic Leukaemia, Chronic Myeloid Leukaemia, and Acute Leukaemia per Million Living, England and Wales,* 1945–9, 1950–4, *and* 1955–7 *; Subdivided by Age*

Age (Years)	Chronic Lymphatic Leukaemia			Chronic Myeloid Leukaemia			Acute Leukaemia			Total Leukaemia		
	1945–9	1950–4	1955–7	1945–9	1950–4	1955–7	1945–9	1950–4	1955–7	1945–9	1950–4	1955–7
15–	0·0	0·0	0·0	0·4	0·4	1·3	16·3	16·7	15·8	16·7	17·1	17·0
20–	0·9	0·2	0·0	1·0	2·1	0·0	10·8	12·3	14·9	12·7	14·6	14·9
25–	0·4	0·4	0·3	2·4	1·7	2·9	10·1	13·5	17·3	12·9	15·6	20·5
30–	0·5	0·5	0·0	3·7	2·5	1·5	13·0	13·2	17·0	17·1	16·3	18·5
35–	0·8	1·3	0·3	3·5	3·9	3·2	16·7	16·5	17·6	20·9	21·7	21·1
40–	2·3	1·7	1·4	6·0	4·6	6·9	16·0	24·6	21·5	24·3	30·9	29·8
45–	3·8	2·2	2·6	8·1	7·4	10·6	20·6	22·6	24·4	32·6	32·2	37·5
50–	3·5	6·4	4·6	9·4	12·2	8·8	22·6	24·8	29·9	35·5	43·3	43·3
55–	8·4	10·5	9·2	13·9	17·0	12·2	22·1	34·0	38·1	44·3	61·5	59·4
60–	12·9	18·4	16·6	15·4	21·9	21·0	32·7	36·6	46·2	61·0	77·0	83·8
65–	18·1	25·3	19·4	20·3	28·6	26·3	32·8	51·0	57·3	71·2	104·8	103·0
70–	24·3	39·0	42·9	19·2	30·9	34·8	28·4	46·8	56·5	71·9	116·6	134·2
75–	21·3	40·9	57·6	18·5	39·3	32·7	21·2	41·6	68·7	60·9	121·8	159·2
80+	22·0	36·9	50·3	14·5	23·3	35·6	6·2	27·7	42·2	42·7	87·9	128·1
All ages	5·3	8·3	8·3	7·7	10·3	9·7	19·1	25·6	27·0	32·1	44·2	45·1

which were described simply as leukaemia was, however, small—of the order of 10% in each age group in 1945–9, 3% in 1950–4, and 2% in 1955–7—and any error due to the wrong allocation of cases in this group cannot have been large. The main possibility of error lies in the classification of the fairly large proportion of cases which were described as lymphatic or myeloid leukaemia, without reference to the clinical type. The age distribution of these cases was, however, intermediate between the age distributions of the acute and chronic cases, and they cannot have consisted wholly of cases of one type. Apart from the oldest age groups, the rates attributed to these types of leukaemia were fairly constant in the three periods studied and the allocation of the unspecified cases to acute and chronic leukaemia in other proportions would have little effect on the apparent trends in the mortality, so long as the proportion remained the same at each period. The estimated mortalities for the three types of leukaemia may not be exact, but the patterns of mortality are similar to those reported for morbidity by MacMahon and Clark (1956), and it is reasonable to believe that they will not require serious modification.

General Aetiological Considerations

It is uncertain whether the increase in the mortality from leukaemia shown in Figs. 1–4 reflects a real increase in the incidence of the disease. The greater increase at older ages could be a cohort effect; that is, it may have resulted from the introduction of a new leukaemogenic agent at some time in the past, such that it is only recently that men and women can have reached the old age groups and yet have been exposed to the new agent at a susceptible period of their lives. There has, however, been no equivalent increase at younger ages previously, and it seems more likely that much of the increase at age 65 years and over is due to improvements in diagnosis and in death certification. A large increase in mortality at these ages has been recorded for several other causes of death (for example, cancer of the lung and gastric ulcer) and a large decrease has been observed in the deaths attributed to senility. Between 1947 and 1956 (the mid-years of the first and the last of the periods studied) the death rate attributed to senility fell from 97 to 8 per million at ages 65–69 years, from 872 to 252 per million at ages 70–74 years, from 3,885 to 1,420 per million at ages 75–79 years, and from 18,689 to 8,586 per million at age 80 years and over. There has therefore been ample opportunity for an increase to be recorded in the mortality from more specific causes of death at these ages, solely as a result of more detailed and more accurate death certification.

If the changes in mortality at the older ages are ignored, it must be concluded that the data obtained in this study show no evidence of any real change in the incidence of chronic lymphatic leukaemia over the past 13 years. In contrast, the data for acute leukaemia suggest that there has been an increase in the mortality of approximately one-third at all ages under 65 years and in both sexes, and it is reasonable to regard this increase as being largely due to a real increase in the incidence of the disease. It may, however, be considered that the diagnosis of acute leukaemia is more sophisticated than that of chronic lymphatic leukaemia, and that consequently the diagnosis of acute leukaemia has not been made as often as it should until the last few years. The data for chronic myeloid leukaemia are difficult to assess. The estimated rates show an increase at most ages for men which is comparable with the increase for acute leukaemia. There is, however, no similar trend in the female rates, and, in view of the small number of cases on which the rates at the younger ages are based in the last period, it seems preferable to suspend judgment on the trend for this type of leukaemia until more data are available.

The sharp differences revealed in the sex ratio of the mortality rates and in the rate of change in mortality with age provide evidence that the causes of the three types of leukaemia are distinct. The relationship between age and the death rate from chronic lymphatic leukaemia is identical with that recorded for most epithelial tumours: for the purposes of comparison the relationship between age and death rate for cancer of the stomach and for chronic lymphatic leukaemia is shown in Fig. 5. This type of relationship is consistent

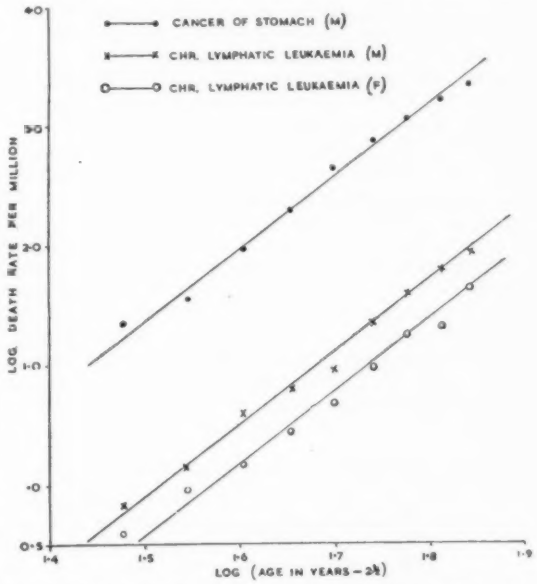


FIG. 5.—Relationship between age and estimated mortality from chronic lymphatic leukaemia in men and in women in 1955–7 compared with the relationship observed for cancer of the stomach in men in 1956. The logarithm of the death rate per million persons is plotted against the logarithm of the age less 2½ years, for ages 30 years to 74 years. The straight line through the points has been drawn arbitrarily to give the best fit, subject to the gradient being 6 to 1 (Armitage and Doll, 1954, 1957).

with a mechanism of cancer induction which takes place in two or more stages and which results in a long latent period (Armitage and Doll, 1954, 1957). The relationships for chronic myeloid leukaemia and for acute leukaemia are in sharp contrast. In none of the epithelial cancers which have so far been examined is the rate of increase in mortality in middle age so slow. This difference may perhaps be related to the finding that the average latent period for radiation-induced leukaemia (characteristically acute leukaemia, and, to a less extent, chronic myeloid leukaemia) is shorter than for other types of cancer, being of the order of four to eight years.

The rate of increase with age which is estimated for acute leukaemia is only slightly less than that for chronic

myeloid leukaemia, but the real difference may be appreciably greater. Some cases of chronic myeloid and chronic lymphatic leukaemia terminate in an acute phase, and it is possible that cases which are first diagnosed in this phase may be recorded as acute when they are really chronic. Since the mortality from chronic lymphatic leukaemia increases rapidly with age, any error of this sort would tend to inflate the mortality attributed to acute leukaemia disproportionately at the older ages, and it is possible that the true incidence of acute leukaemia increases with age after the age of 30 years even more slowly than has been estimated.

In none of the three types of leukaemia is the relationship between age and mortality similar to that recorded for the hormone-dependent tumours (Armitage and Doll, 1954), and this is evidence that the difference in the sex ratios is not dependent upon hormonal factors. The differences may therefore be regarded as depending on differences in the degree to which men and women are exposed to external leukaemogenic agents. It follows that the principal causes of chronic lymphatic leukaemia are likely to be such that in England and Wales men are exposed to them two to three times more heavily than women. In contrast, men and women must be equally or nearly equally exposed to the principal causes of chronic myeloid and acute leukaemia.

The one major difference between chronic myeloid and acute leukaemia is that the mortality from acute leukaemia is relatively high in adolescence, and is even higher in childhood—for nearly all leukaemia deaths in childhood are due to acute leukaemia—and that the mortality falls until the age of about 30 years, before it begins to rise. In contrast the mortality from chronic myeloid leukaemia is low in childhood and rises continuously with age from adolescence. This difference might be explained if the two diseases had a common cause which acted through two different mechanisms, or if the principal causes of the two diseases were distinct.

Ionizing Radiations: A Specific Aetiological Factor

Ionizing radiations are the only leukaemogenic agents for which there is convincing epidemiological evidence that they affect man. It is also certain that there has been an appreciable increase in the exposure to the general population, particularly from *x* rays in medical diagnosis, and that men and women have probably been equally affected. The extent to which this exposure may be responsible for at least some of the recorded increase in leukaemia mortality has been the subject of controversy.

On the one hand, on the basis of a hypothesis that even the smallest doses of radiation can be leukaemogenic, it has been supposed that some cases result from the use of *x* rays in diagnosis (Stewart, Webb, Giles, and Hewitt, 1956; Court Brown and Doll, 1957). The hypothesis was put forward from studies of (1) histories given by the mothers of children who died of malignant disease, and (2) the relationship between the dose and leukaemia incidence in patients treated with *x* rays for ankylosing spondylitis. In the latter study one interpretation of the data was that over the lower ranges of dose the relationship might be linear, and that there might be no level of dose below which cases did not occur. If this was so, it would seem likely that some cases of leukaemia develop on the basis of a gene mutation. On the other hand, an alternative view has been summarized by Loutit (1958), who says of the above hypothesis that it is based on "a theory of carcinogenesis that has been discussed for many years and found wanting, certainly as a sole cause." Loutit adds that "the theory would also require that leukaemia be increased in incidence with increasing age and accumulation of radiation dose from natural radiation. In fact, certain statistics show that only chronic lymphatic leukaemia increases in this way, and this is the only type of leukaemia which historically has not been linked with radiation."

It has not previously been possible to study the age-specific death rates for the different types of leukaemia sumultaneously with the trends in these death rates with time. The results of this present study are of interest in that they have a bearing on the above controversy and they may go some way towards resolving it.

It has been shown, for each of the three periods studied and for each of the three different classes of leukaemia, that there is an appreciable increase in mortality with age during a large part of adult life. There is, however, an important difference in the trends of the mortality rates with time. Thus in each age group the mortality of acute leukaemia has increased between 1945 and 1957, whereas the mortality from the chronic leukaemias, with the exception of chronic myeloid leukaemia in men, has increased during the period of observation only in the older age-groups. At these ages the mortality has increased for all types of leukaemia in both sexes, but the increase in chronic lymphatic leukaemia in men has been outstanding. It is suggested that the observed increase in the age-specific death rates of acute leukaemia at ages under 60 years is largely real and due to increasing exposure of the population to leukaemogenic factors in the environment, but that most of the increase in the death rate from the chronic leukaemias is due to their better recognition consequent upon improved medical care for the elderly.

In this context it is important to note the evidence that radiation exposure has been associated with an increase in acute leukaemias more often than with chronic myeloid leukaemia, and not at all with an increase in chronic lymphatic leukaemia. Thus of the 50 cases which have occurred to date in the spondylitis series, inclusive of the 41 cases originally reported (Court Brown and Doll, 1957), no fewer than 38 have been examples of the acute disease and only 8 chronic forms have been found, the data in the remainder being insufficient to determine the clinical type. Only one of the eight chronic leukaemias was lymphatic in type. Similar results have been observed among the survivors of the atomic explosion at Nagasaki, but cases of chronic myeloid leukaemia have been reported with about the same frequency as cases of the acute disease among the survivors at Hiroshima (Wald, 1957).

The extent to which the increases in the national mortality rate from acute leukaemia may be related to increases in our artificial radiation background can be adequately assessed only with greater knowledge of the basic mechanisms of cancer induction and of the relationship between radiation dose and incidence. If, however, a leukaemic process can be initiated not only by a gene mutation but also, and possibly more frequently, by a complex genetical disturbance depending on gross chromosome damage, then the more important physical factor may be the rate at which a

radiation dose is given rather than the total dose. In this case it could be important that radiation for medical purposes is given at high dose rates in the approximate range of 40 to 100 r a minute, while the average dose rate from natural background radiation is 2×10^{-6} r a minute.

Summary and Conclusions

The deaths from leukaemia in England and Wales for the period 1945 to 1957 have been classified under three headings—acute leukaemias of all types, chronic myeloid leukaemia, and chronic lymphatic leukaemia. The age-specific mortality rates have been calculated for each type of leukaemia, for each sex, and for three periods of time—1945 to 1949, 1950 to 1954, and 1955 to 1957.

A study of these data suggests that the principal feature in the real increase in leukaemia is a change in the incidence of acute leukaemia. This is compatible with the concept that an increased exposure to ionizing radiations plays some part in the changed incidence of the disease.

We are indebted to the Registrar-General of England and Wales for the extraction of the data and for permission to publish the results, and to Miss F. Callaby, Mrs. A. Frackiewicz, Mrs. E. A. O. Gray, and Mrs. V. Peetz for their assistance in the analysis.

REFERENCES

Armitage, P., and Doll, R. (1954). *Brit. J. Cancer*, **8**, 1.
—— —— (1957). Ibid., **11**, 161.
Burnet, M. (1958). *New Engl. J. Med.*, **259**, 423.
Clemmesen, J., and Sørensen, J. (1958). *Dan. med. Bull.*, **5**, 73.
Court Brown, W. M., and Doll, R. (1957). *Spec. Rep. Ser. med. Res. Coun. (Lond.)*, No. 295.
Hewitt, D. (1955). *Brit. J. prev. soc. Med.*, **9**, 81.
Loutit, J. F. (1958). *Practitioner*, **181**, 553.
MacMahon, B., and Clark, D. (1956). *Blood*, **11**, 871.
Registrar-General of England and Wales (1958). *Statistical Review of England and Wales for the Year 1956. Part III. Commentary*. H.M.S.O., London.
Stewart, A., Webb, J., Giles, D., and Hewitt, D. (1956). *Lancet*, **2**, 447.
Wald, N. (1957). *Acta haemat. jap.*, **20**, 152.
World Health Organization (1955). *Epidem. vital Statist. Rep.*, **8**, 81.

On April 27 England and Wales will have new standards for ice-cream. The main changes made by the new regulations are that standards are to be fixed for dairy ice-cream and for milk ice which are required to contain milk fat and must not contain any other fat; that saccharin and other artificial sweeteners are not to be used in any ice-cream or in milk ice, and no mimimum sugar content is laid down; that ice-cream made with non-milk fat is not to be labelled or advertised in a way which is suggestive of butter, cream, or milk; but such ice-cream may continue to be sold as "ice-cream" and it may bear a statement that it contains skimmed milk solids; that, after November 30 of this year, all pre-packed ice-cream which is made with non-milk fat must be labelled as containing vegetable or non-milk fat if it is sold as "ice-cream." The present requirements that ice-cream must contain not less than 5% fat and not less than 7½% milk-solids-not-fat are included in the new regulations and so continue in force. The new regulations will revoke and replace the existing Food Standards (Ice-Cream) Order, 1953. The Secretary of State for Scotland proposes to make corresponding regulations which will apply in Scotland.

P.T.C. TASTE RESPONSE AND THYROID DISEASE

BY

F. D. KITCHIN, M.B., M.R.C.P.

W. HOWEL-EVANS, M.D., M.R.C.P.

From the Thyroid Clinic, David Lewis Northern Hospital, Liverpool

C. A. CLARKE, M.D., F.R.C.P.

R. B. McCONNELL, M.D., M.R.C.P.

AND

P. M. SHEPPARD, M.A., D.Phil.

From the Departments of Medicine and Zoology, University of Liverpool

For over a hundred years a familial disposition in thyroid disease has been known. Since Romberg (1851) recorded Graves's disease in twins there have been many genetic studies using the classical method of pedigree analysis, but the results have been conflicting. Bartels (1953), on the basis of his own work (Bartels, 1941) and a review of the literature, concluded "that sporadic thyroid affections such as simple goitre, hypothyroid, and hyperthyroid states are probably genetically determined."

Fox (1932) discovered that some people taste phenylthiocarbamide (P.T.C.) and others do not. Further investigation established that this bimodal taste response was an example of human genetic polymorphism; about 30% of Europeans and white Americans were non-tasters and 70% were tasters (Barnicot, 1950; Harris and Kalmus, 1950a).

In 1942 Richter and Clisby noticed marked thyroid hyperplasia in rats which had been fed with P.T.C., and subsequent work has established that the thiocarbamides in general are active goitrogenic substances. Among them are to be found the thiouracils as well as some naturally occurring goitrogens which have been isolated from turnips, brussels sprouts, rape, and kale, and found to belong to the same chemical family—all having the $-N-C-$ grouping.
$\quad\quad\quad

diffuse goitre who had not been operated on (see below). The majority of the patients lived on Merseyside, which is not an area of endemic goitre.

The control group of 265 subjects was constructed by taste-testing hospital nurses and university students. The mean age of the control group (21.2 years) was some 10–20 years younger than the patient group, but, as age does not influence the distinction between tasters and non-tasters, this was not regarded as disadvantageous. However, with increasing age there is a slight loss of taste sensitivity to P.T.C. (Harris and Kalmus, 1950a), and this is commented on later.

Methods

Taste-testing

The P.T.C. taste response was determined by the method of Harris and Kalmus (1950a), and is based on the ability of individuals to discriminate various dilutions of the test substance from water.

Starting from a high dilution and working down, the subject tastes a few millilitres of the solutions until a definite taste is perceived. At high dilutions this substance in a "taster" is appreciated on the posterior surface of the tongue and pharynx, and thus patients are asked to swallow the solution intact instead of retaining it in their mouths and so diluting the solution with saliva. Having found an approximate threshold, the subject is then given eight glasses—four containing the P.T.C. solution at the concentration shown in the preliminary test, and four containing water. The eight glasses are arranged at random and the subject is asked to separate the two groups. If this is done correctly a further eight-glass trial is made at the next weaker dilution, but if the subject is unable to separate the two groups accurately the test is repeated with increasing concentrations of P.T.C. until a threshold is obtained.

At the time the taste-testing was performed (by either F.D.K. or W.H.E.) the nature of the goitre was unknown to us. Further data concerning the family history and the domicile were obtained and a specimen of saliva was also taken for determination of the secretor character (see Clarke *et al.*, 1956).

In addition, 15 patients were taste-tested before and after thyroidectomy to determine whether any change in the threshold occurred and also to check the accuracy of the tasting method in our hands. In 11 of the 15 patients retested the taste threshold was unaltered, in two patients there was a change of threshold of one dilution (6 to 7 and 7 to 8), and in two patients a change of two dilutions (6 to 8 and 11 to 9). Thus in no instance did this slight alteration affect the distinction between tasters and non-tasters.

Classification

The classification of thyroid disease adopted was as follows: Group 1: single adenoma (*a*) toxic ("hot nodule"), (*b*) non-toxic. Group 2: multiple adenoma (*a*) toxic ("secondary thyrotoxicosis"), (*b*) non-toxic. Group 3: diffuse goitre (*a*) toxic ("primary thyrotoxicosis"), (*b*) non-toxic. This was similar to that used by Harris *et al.* (1949) except for the separation of single adenomata into group 1, as a result of a discussion with Dr. Trotter (personal communication, 1956). Further comments on this group are made later. The term "adenoma" is retained although these nodules, usually multiple, are known to be the result of recurring cycles of hyperplasia and involution.

Diagnosis

At a later date, when the P.T.C. testing had been done, the diagnosis in each patient was made after considering the following evidence: (*a*) clinical features and the course of the disease; (*b*) the operative findings; (*c*) the macroscopic and microscopic findings in the thyroid of the operative specimen; and (*d*) ^{131}I studies in many instances.

It should be emphasized that the data outlined above were available for each person in this series, since the patients were attending an established special clinic.

Patients who had undergone thyroidectomy were chosen, as examination of the excised gland provides more precise information than clinical examination alone. This was done in view of the fact that many thyroid adenomata are impalpable and that either exaggerated lobulation of a diffusely hyperplastic gland or the gland in thyroiditis may simulate multiple adenomata. In addition, because group 3*a* was small, we added eight typical cases of toxic diffuse goitre in young people who had not been operated upon. This could be done because the diagnostic error is much smaller here than with multiple adenomatous goitre.

To keep personal error and bias to the minimum each case was assessed by two of us (W. H. E. and F. D. K.), and the final diagnosis was made only after joint discussion but without knowledge of the taste threshold.

We appreciate that accuracy of diagnosis is crucial in an investigation of this sort. By analysing each case by the methods shown above, we consider that error has been reduced to a minimum, although clearly not eliminated. As expected with such criteria it was found impossible to establish a diagnosis in 16 patients in this series, and these are excluded from the analysis. They have, however, been included in the tables to show the taste threshold distribution.

Comment on Group 1*b*

This group of cases in which a single nodule was found is especially liable to errors in diagnosis. Great care was taken to check the histological pattern, since we felt that many pathological states could mimic a single nodule. On gross and microscopical examination the group was found to consist of the following morphological types: (*a*) colloid adenoma, mainly macro-acinar (29 cases); (*b*) cystic adenoma, due to degeneration (5 cases); (*c*) fleshy adenoma, mainly micro-acinar (8 cases); (*d*) papillary adenoma, borderline malignant (1 case). Types *a* and *b* may be the result of a localized hyperplastic/involution process which may eventually become widespread throughout the gland.

In the thyroid, although hyperplastic areas are difficult to distinguish from neoplastic proliferation, types *c* and *d*, in our view, exhibit the features of neoplasia rather than of hyperplasia. However, in view of the small numbers involved this group has not been subdivided.

Results

Table I shows the basic data of the thyroid patients and the control group. It will be seen that the former are divided into their appropriate diagnostic categories.

Table II gives the P.T.C. threshold distributions of all the individuals in Table I, together with those of the 16 unclassifiable patients mentioned above. The histograms (Figs. 1 to 4) show diagrammatically the taste distributions of the main groups.

TABLE I.—*General Data on Goitre and Control Distribution*

	Group 1		Group 2		Group 3		Controls
	a	*b*	*a*	*b*	*a*	*b*	
Total No. in groups ..	2	43	30	216	133*	7	265
Female	1	38	27	191	112	6	210
Male	1	5	3	25	21	1	55
Mean ages in years ..	46·2		46·0		39·4	31·4	21·2
Age range ,, ,, ..	18–70		15–80		14–60	20–45	19–50
Domiciled in Liverpool and Wirral areas ..	75%		65%	66%	65%	70%	46%
Parents or sibs with goitre	20%		33%	33%	16%	42%	6%

* Includes 8 non-operation cases.

Statistical Analysis

The dividing line between tasters and non-tasters has been taken as being between serial dilutions 4 and 5, since all the data are consistent with there being an antimode in the region of dilution 4. There is no significant difference in the frequency of non-tasters between males and females of the control group, and the frequency is consistent with other investigations in England (Barnicot, 1950; Harris and Kalmus, 1950a). A slight excess of non-tasters is usually found in males and is of the order observed here. However, a significant difference would not be expected from a sample of the present size.

There is also no evidence of heterogeneity between males and females with respect to the frequency of non-tasters in the toxic diffuse goitre and single adenoma categories. However, in the multiple adenoma class there are about twice as many non-tasters among the males, and this sex difference is highly significant (see Table III). Consequently, in the subsequent analysis the sexes have been treated separately in this disease group. A comparison between the toxic and non-toxic conditions within this category shows that there is no significant difference between males and females.

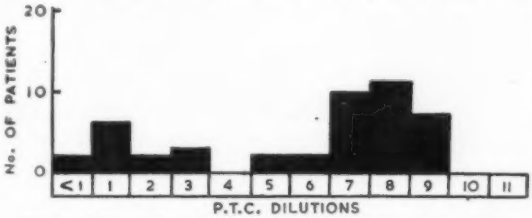


FIG. 1.—Groups 1*a* and 1*b*: Single adenoma. 45 patients.

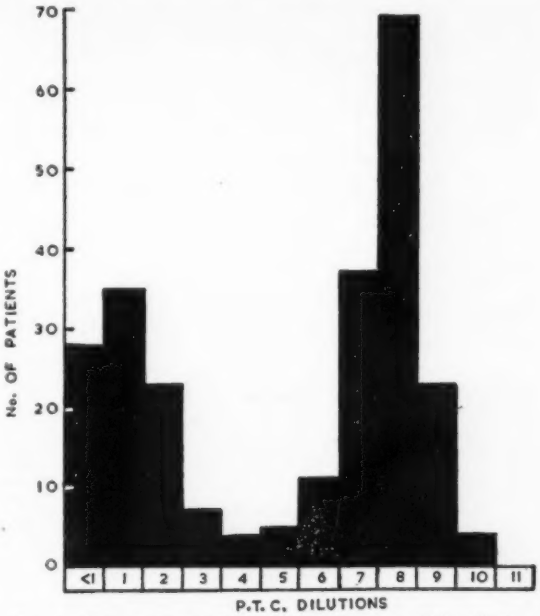


FIG. 2.—Groups 2*a* and 2*b*: multiple adenoma. 246 patients.

Compared with the control population there is a highly significant deficiency of non-tasters among people with toxic diffuse goitre and an excess among those with multiple adenomata, the excess being significantly more marked in the males. As would be expected, therefore, the males and females with toxic diffuse goitre and those with multiple adenomata are very different from one another with respect to the frequency of non-tasters. The single adenoma category is not different from the controls and toxic diffuse goitre categories, nor is there heterogeneity between the females of this group and those with

TABLE II.—*Data on Taste Threshold in Goitres and Controls*

Group		Total	Tasters	Non-tasters	*P.T.C. Dilutions*												
					<1	1	2	3	4	5	6	7	8	9	10	11	12
1*a*		2	1	1	1 F	—	—	—	—	—	—	—	—	1 M	—	—	—
1*b* Male		5	5	—	—	—	—	—	—	2	—	—	2	1	—	—	—
1*b* Female ..		38	26	12	1	6	2	3	—	—	2	10	9	5	—	—	—
	Total ..	43	31	12 (27·8%)	1	6	2	3	—	2	2	10	11	6	—	—	—
1*a*+*b* ..	Total ..	45	32	13	2	6	2	3	—	2	2	10	11	7	—	—	—
2*a* Male		3	—	3	2	1	—	—	—	—	—	—	—	—	—	—	—
2*a* Female ..		27	18	9	4	3	2	—	—	—	1	5	7	3	2	—	—
	Total ..	30	18	12 (33·3%)	6	4	2	—	—	—	1	5	7	3	2	—	—
2*b* Male		25	10	15 (60%)	5	7	3	—	—	1	—	3	6	—	—	—	—
2*b* Female ..		191	121	70 (36·6%)	17	24	18	7	4	4	10	29	56	20	2	—	—
	Total ..	216	131	85 (39·35%)	22	31	21	7	4	5	10	32	62	20	2	—	—
2*a*+*b* ..	Total ..	246	149	97 (39·3%)	28	35	23	7	4	5	11	37	69	23	4	—	—
3*a* Male		18	15	3	—	2	—	1	—	—	2	5	7	1	—	—	—
3*a* Female ..		107	89	18	3	4	8	1	2	3	3	31	45	7	—	—	—
	Total ..	125	104	21 (15·8%)	3	6	8	2	2	3	5	36	52	8	—	—	—
3*a* clinical only ..	..	8	7	1	—	1	—	—	—	—	—	2	2	3	—	—	—
3*a* operative+clinical ..		133	111	22 (16·6%)	3	7	8	2	2	3	7	38	55	8	—	—	—
3*b*	..	7	5	2	—	1 M	—	1	—	1	—	—	2	2	—	—	—
Rejected group, diagnosis impossible ..	..	16	11	5 (31·2%)	1	2	1	1	—	—	2	5	1	2	1	—	—
Controls Male ..	..	55	36	19	6	10	—	1	2	3	2	2	16	9	4	—	—
Controls Female ..	..	210	151	59	8	33	14	3	1	7	3	15	50	57	15	1	3
	Total ..	265	187	78 (29·4%)	14	43	14	4	3	10	5	17	66	66	19	1	3

TABLE III.—*Statistical Analysis*

Comparison	χ^2	D. of F.	P
Control ♂–♀	0·69	1	>0·3
Single adenoma (group 1*b*) non-toxic ♂–♀	—	—	>0·1
Multiple adenomata			
(Group 2*a*) toxic ♂–♀	—	—	>0·05
(Group 2*b*) non-toxic ♂–♀	4·12	1	<0·05
♂ toxic–non-toxic	—	—	>0·2
♀ ,, ,,	0·11	1	>0·7
♂ toxic+non-toxic ♂–♀	7·04	1	<0·01
Toxic diffuse goitre (group 3*a*)			
Operative series: ♂–♀	—	—	>0·5
Clinical series: ♂–♀	—	—	>0·5
Operative—clinical series	—	—	>0·5
Single adenoma (group 1*b*):			
Non-toxic–control	0·04	1	>0·8
Multiple adenomata (group 2)			
♂ toxic+non-toxic–control ♂	5·80	1	<0·02
♀ ,, ,, ,, ♀	2·77	1	>0·05
	8·57	2	<0·02
Toxic diffuse goitre (all cases) (Group 3*a*):			
Toxic—control	7·15	1	<0·01
Toxic diffuse goitre (all cases):			
♂ toxic—multiple adenomata ♂ toxic+non-toxic	—	—	<0·001
♀ ,, ,, ♀ ,, ,,	12·26	1	<0·001
Single adenoma:			
♂ non-toxic—multiple adenomata ♂ toxic+non-toxic	—	—	<0·013
♀ non-toxic—multiple adenomata ♀ toxic+non-toxic	0·14	1	>0·7
Single adenoma:			
Non-toxic—toxic diffuse goitre	2·01	1	>0·1

multiple adenomata. However, the males are significantly different from the multiple adenomata males, having a lower frequency of non-tasters.

When considering the nature of the association revealed by the statistical analysis it is necessary to take into account the mean age in the various categories since it is known that sensitivity to P.T.C. decreases with age. Consequently, by taking the dividing line between tasters and non-tasters of all groups as falling between dilutions 4 and 5, one might obtain a difference in the frequency in non-tasters which results merely from a difference in the mean age of individuals in the categories and does not reflect a genetic diversity. A χ^2 analysis of the numbers of individuals in each dilution group within the taster class (combining dilutions 5 with 6 and 9 with 10 because of small numbers) reveals that there is no significant heterogeneity between the diffuse goitre, single adenoma and multiple adenomata categories ($\chi^2_6 = 10.3$, $P > 0.1$). We are therefore safe in concluding that the highly significant differences between the toxic diffuse and multiple adenomata categories reflect a real genetic difference and are not caused by a general decrease in sensitivity to P.T.C. with age.

FIG. 3.—Group 3*a*: 133 patients.

The control group has a lower mean age than the total goitre group and therefore might be expected to be more sensitive to P.T.C. Any discrepancy resulting from this would mean that the control group would have to be adjusted to contain more non-tasters; consequently the significant difference between the controls and diffuse goitre categories would be enhanced and not reduced. In fact, a χ^2 analysis reveals that within the taster class there is a very significant difference between the combined goitre and control group ($\chi^2 = 79.7$, $P < 0.001$), the mean threshold dilution being 8.3 for the control but only 7.6 for the goitre groups, as would be expected from the greater mean age of the latter. However, a more detailed analysis reveals that the shift in sensitivity with age is not the same at all dilutions, being far greater in the higher dilutions and smaller in the region of thresholds 4 and 5. This is revealed in part by the heterogeneity χ^2 in which dilutions 9 and 10 together supply nearly two-thirds of the value of the χ^2. Almost the same proportion is contributed to the heterogeneity χ^2 within the combined goitre group by the highest dilution—namely, 9 and 10 combined.

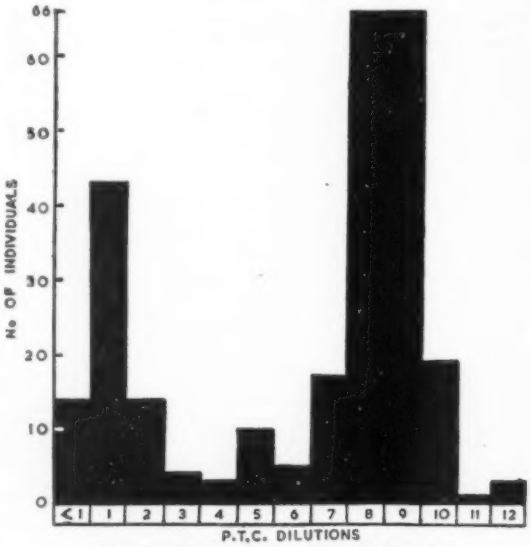


FIG. 4.—Control group: 265 individuals.

The greater change at higher dilutions can be partly adjusted for if one assumes that 0.1 times the dilution is the compensation factor which should be applied to the control group at each dilution. For example, all the individuals at dilution 10 will be placed in dilution 9, but only 0.5 of those in dilution 5 will be transferred to 4, the non-taster category. Such an adjustment removes the heterogeneity between the goitre and control groups, and the change of five individuals from the taster controls to the non-tasters does not invalidate the statistical conclusions on goitre. In fact, it is evident from the data that such a large adjustment as five

individuals between the taster and non-taster categories is unwarranted, since it is quite clear that the figure 0.1 should itself be reduced at lower dilutions.

Further evidence of the absence of misclassification due to an age effect between tasters and non-tasters comes from the multiple adenomata category. There is no increase in the incidence of non-tasters with age (range 15–80 years), demonstrating that there can be no significant tasting error.

We can conclude that, despite the circumstance that our control group was younger than the goitre group, the differences confirmed by statistical analysis reflect real differences in genotype frequencies and are not just a consequence of age.

Blood Group and Secretor Data (Table IV)

Analysis shows that there is no significant heterogeneity between the blood-group distributions, the frequencies of non-secretors in the three main groups of thyroid disease combined, and the controls ($P>0.1$; $P>0.2$ respectively). We can say, therefore, that the data show no evidence that there is an association between these characters and the varieties of thyroid disease examined. Further, the figures support the view that the goitre subjects and controls were drawn from comparable populations.

TABLE IV.—*Blood Groups and Secretor Status*

Phenotype	Group 1	Group 2		Group 3	Controls
	a+b	*a*	*b*	*a*	
O S	9	10	68	35	81
O ss	3	2	28	12	28
A S	13	9	49	22	54
A ss	8	1	12	17	24
B S	—	2	14	9	12
B ss	—	—	4	4	3
AB S	1	—	4	4	4
AB ss	—	—	—	1	2
Total ..	34	24	179	104	208
	% ss=32·5	% ss=23·1		% ss=32·7	% ss=27·7

Discussion

An abnormal taste distribution has been found in two main groups of patients with thyroid disease—those with multi-adenomatous goitre, both toxic and non-toxic, and those with toxic diffuse goitre. Before ascribing a causal relationship to the associations, four considerations must be borne in mind.

1. *Biased Diagnosis.*—Although care was taken to avoid bias, occasionally the nature of the goitre might have been remembered when taste-testing was carried out. Consequently, it is possible that there was a subconscious bias in assigning a score to people in thresholds lying in the region of 5. However, the score assigned depended on the reactions of the patient to various solutions and not on the observer. Moreover, retesting has shown little error in the technique, and owing to the small numbers of people in thresholds 3, 4, and 5, the bias would have to be enormous. We therefore believe that such an effect cannot account for the associations. The other possibility, which is more difficult to assess, is that there was bias in the diagnosis of the type of goitre if the taste threshold was remembered. In fact, although it might be fairly easy to remember the diagnosis of the goitre in patients who had attended the clinic regularly, the chances of remembering the taste threshold, which was usually ascertained only once, would be much smaller. Moreover, there seems no reason for remembering the thresholds of males rather than those of females, so the sex difference cannot be accounted for in this way. It seems fairly certain, therefore, that neither of these biases materially affects the result.

2. *Incorrect Diagnosis.*—In such a difficult field as goitre diagnosis there are bound to be some errors, and it is impossible to assess the magnitude of these. However, mistakes in diagnosis, provided they are not biased as a result of the knowledge of the taste threshold, could not, on their own, manufacture a statistical association with this genetic marker. In fact, they would obscure the association, and consequently the relationship between tasting and goitre cannot solely be due to errors in diagnosis.

3. *Difficulties in Diagnosis.*—We were unable to establish a diagnosis in 16 out of this series of 447 patients, 6 of these patients exhibiting in the thyroid gland macroscopic and microscopic features of diffuse hyperplasia with localized adenomatous change. However, this proportion is small and constitutes only 3.5% of the whole series. Merely excluding difficult cases without reference to their taste threshold could not give rise to an association between tasting and nodular or diffuse goitre if none really existed.

4. *Racial Stratification.*—It is conceivable that within the population there are strata which are high or low in the frequency of tasting and which also differ in the type of goitre they develop without the two being related. The association between the nature of the goitre and the frequency of the taster/non-taster classes can hardly result from an undetected stratification of this type within the English population. Not only are the differences too large, but the sex difference within the multiple adenomata group, and the difference between multiple and toxic diffuse goitres, are quite inconsistent with such a hypothesis when the domicile and origins of the individuals in the survey are investigated.

A Causal Relationship

If a causal hypothesis is accepted the results of this analysis indicate that the taster/non-taster genotypes are important in determining the type of thyroid disease which an individual may develop, and that in the multiple adenoma group the genotype is about twice as important in males as in females.

It is improbable, in view of the marked differences in P.T.C. taste response found in toxic diffuse and multi-adenomatous goitre, that the effect in thyroid disease depends solely on the ability or inability to detect the specific bitter and unpleasant taste of the thiocarbamides and so act as a means of avoiding the toxic hazard of natural compounds of this sort. It is more likely that this easily measured action of the gene is only a part of a wider fundamental biochemical action.

From a biochemical standpoint the differential taste response is confined to a group of substances possessing a $-N-C-$ linkage (Harris and Kalmus, 1950b). They

$$-N-C- \quad (\text{with } S \text{ double-bonded to } C)$$

are all active reducing agents, and P.T.C. itself has been shown to inhibit tyrosinase. Their biological action is to inhibit the synthesis of thyroxine. This effect occurs within the thyroid, is uninfluenced by iodine medication, and results in thyroid hyperplasia under the stimulus of pituitary thyrotrophin. One such compound, L.5.vinyl-

2-thio-oxazolidone ("goitrin"), has been isolated from turnips and its presence demonstrated in the seeds of cabbage, rape, kale, and brussels sprouts (Astwood, Greer, and Ettlinger, 1949). Greer (1957) showed that kale seed, of all the members of the mustard family (Cruciferae), contains the largest quantities of this substance.

The finding of this compound in nature stimulated interest in its role in the pathogenesis of goitre, but its clinical importance, in comparison with that of iodine deficiency, is generally thought to be slight. This view was reinforced when it was shown that cooking these vegetables (*Brassica*) destroyed the enzyme system responsible for the formation of the goitrogen from its precursor ("progoitrogen"). It was then noted that brassicae are a source of winter food for cattle and that milk may be the vehicle for the transmission of the goitrogen to man. Clements and Wishart (1956) described an outbreak of goitre among children in Tasmania in an area where iodine prophylaxis had been practised carefully. They demonstrated a goitrogen, which they were unable to identify, in the milk from cows which had been fed on kale (choumoellier) but not in milk from cows fed on fodders which did not contain either brassicae or kale.

In this country Greene, Farran, and Glascock (1958) confirmed these findings experimentally in rabbits fed on kale milk, but they were unable to demonstrate significant depression of serial ^{132}I uptake curves in seven healthy men after one month of taking milk from kale-fed cows. In our opinion the ^{132}I method is not comprehensive enough to exonerate the role of kale milk as a goitrogen in man, particularly in view of the previous finding of Clements and Wishart (1956).

The results of this survey in adenomatous goitre naturally suggest the hypothesis that the inability to taste P.T.C. is associated with a greater susceptibility to the action of goitrogens of a similar chemical type, and cows' milk could be an important source of such compounds in the winter months. If this were so, cycles of seasonal involution and hyperplasia would occur in the thyroid, particularly in non-tasters of P.T.C., and it is just this pathological sequence which is known to give rise to adenomatous goitre in later life.

A notable finding in the series of adenomatous goitres is the considerably higher incidence of non-tasters of P.T.C. in the male as compared with the female patients. The male : female ratio in sporadic goitre lies between 1 : 8 and 1 : 15, except in areas of endemic goitre, where the sex ratio approaches unity. In view of the fact that, in the female, cyclical changes of involution and hyperplasia are known to occur in the thyroid in relation to the menstrual cycle and child-bearing, it might be anticipated that genetic influences (other than those affecting sex) would be less important in women than in the male. Our findings show this clearly, the incidence of non-tasting in the males with adenomatous goitre being 60%, in contrast to the female rate of 36.6%.

It remains to consider the association between tasting and diffuse goitre, a finding which was not reported by Harris *et al.* (1949). If the association we have found is real it seems likely that the taster status determines the nature of the goitre—that is, whether it be nodular or diffuse. If the hypothesis that non-tasters are more susceptible to thiocarbamides is correct, it seems possible that the homozygote tasters (TT) are even less susceptible than the heterozygotes (Tt). Such insusceptibility would then have to be assumed to render the gland more prone to toxic diffuse goitre, and thus one of the natural restraining mechanisms in thyroid homoeostasis is removed. This could result in a highly sensitive gland which might react more vigorously to psychic stimuli via the medium of the pituitary and hypothalamus. The data are not of a sort to test this hypothesis, but it is capable of experimental verification. Whether these hypotheses are correct or not, the associations described make it possible to attack the pathogenesis of all types of non-endemic goitre from a new angle.

Summary

The P.T.C. taste threshold was determined in 447 patients with thyroid disease and in a control group of 265 individuals by the eight-glass technique of Harris and Kalmus.

In 246 cases of adenomatous goitre, a significantly high incidence of non-tasters (genotype tt) was found, and this was proportionately greater in men (60%) than in women (36.6%).

In 133 patients with toxic diffuse goitre a significant excess of tasters was found (genotypes TT, Tt), but without sex difference.

The findings suggest that the taster/non-taster genotypes are of importance in determining the type of thyroid disease, and the possible mechanisms are discussed.

The distribution of the ABO blood groups and secretor status in multi-adenomatous and toxic diffuse goitre was not found to differ significantly from that of the control group.

We thank Mr. Philip Hawe and Dr. W. H. R. Cook for allowing us full access to their patients and for encouraging us to do this work. We are indebted to Dr. W. Kulke, of the Liverpool Radium Institute, for the isotope investigations. Dr. R. Winston Evans, pathologist at the David Lewis Northern Hospital, Liverpool, has given us invaluable help with the pathological aspects of this survey. We are grateful to Mr. W. T. A. Donohoe for much technical assistance in the serological aspects of the work. To Dr. H. Harris, Dr. H. Kalmus, and Dr. W. R. Trotter our grateful thanks are due for their advice on taste-testing and other aspects of this investigation. Miss Sheila Manning has given us invaluable help throughout, and was responsible also for all the secretarial work. Finally, we wish to thank the Medical Research Committee of the United Liverpool Hospitals, under the chairmanship of Lord Cohen of Birkenhead, the Medical Research Council, and the Nuffield Foundation for their grants towards our genetic research, without which this work could not have been undertaken.

REFERENCES

Astwood, E. B., Greer, M. A., and Ettlinger, M. G. (1949). *Science*, **109**, 631.
Barnicot, N. A. (1950). *Ann. Eugen. (Lond.)*, **15**, 248.
Bartels, E. D. (1941). *Heredity in Graves' Disease*. Munksgaard, Copenhagen.
—— (1953). In *Clinical Genetics*, edited by A. Sorsby, p. 529. Butterworth, London.
Clarke, C. A., Edwards, J. W., Haddock, D. R. W., Howel-Evans, A. W., McConnell, R. B., and Sheppard, P. M. (1956). *Brit. med. J.*, **2**, 725.
Clements, F. W., and Wishart, J. W. (1956). *Metabolism*, **5**, 623.
Fox, A. L. (1932). *Proc. nat. Acad. Sci. (Wash.)*, **18**, 115.
Greene, R., Farran, H., and Glascock, R. F. (1958). *J. Endocr.*, **17**, 272.
Greer, M. A. (1957). *Amer. J. clin. Nutr.*, **5**, 440.
Harris, H., and Kalmus, H. (1950a). *Ann. Eugen. (Lond.)*, **15**, 24.
—— —— (1950b). Ibid., **15**, 32.
—— —— and Trotter, W. R. (1949). *Lancet*, **2**, 1038.
Richter, C. P., and Clisby, K. H. (1942). *Arch. path. (Chicago)*, **33**, 46.
Romberg, M. H. (1851). *Klinische Wahrnehmungen und Beobachtungen*. Hertz, Berlin. Quoted by Bartels (1941).

TREATMENT OF HEART FAILURE IN HAEMOCHROMATOSIS

BY

JOHN EVANS, B.Sc., M.R.C.P., D.P.M.

Former Medical Registrar, Cardiff Royal Infirmary

The first major therapeutic advance in the treatment of haemochromatosis, the use of venesection, was introduced by Balfour *et al.* in 1942 and Finch in 1949, who realized that the excessive iron deposits which produced the disease could be mobilized by repeated bleeding; since then a number of case reports have appeared. The purpose of this paper is to report and discuss the effects of venesection in two cases of haemochromatosis with heart failure and the necropsy findings in one of them. So far as I am aware, only two reports of heart failure in haemochromatosis treated by venesection have been published and only one necropsy report describing a patient treated by venesection has appeared.

Case 1

A sign-painter aged 57 was admitted to St. David's Hospital, Cardiff, on November 10, 1952, for treatment of chronic eczematous dermatitis. During treatment grey pigmentation of his skin was noticed, and it was found that he had had loss of libido and increasing skin pigmentation for 10 years. Hair growth had been slow for some years and there had been attacks of colicky abdominal pains. There were no symptoms of cardiac failure and no abnormality of the cardiovascular system was noted. E.C.G. (Fig. 1) and chest *x*-ray film (Fig. 2) were normal. The liver was enlarged. Skin biopsy showed haemosiderin deposits around the sweat glands. A diagnosis of haemochromatosis was made.

He was admitted to the Cardiff Royal Infirmary on May 2, 1953, having become very breathless during the preceding fortnight. The relevant findings were: orthopnoea, a regular pulse rate of 68 a minute, and a blood pressure unchanged at 110/75, with ascites and bilateral pleural effusions. A chest *x*-ray film showed considerable increase in size of the cardiovascular outline; there was marked reduction of the E.C.G. voltage. The CR leads, recorded for the first time, showed T wave inversion in CR_{4-7} (Fig. 1). Treatment with rest and digitalis was begun.

Between his second admission and his sixth on February 26, 1955, his condition deteriorated. He could walk only 10 yards (9 m.) in the ward before becoming exhausted, and at night required four pillows. At this stage clinical examination showed him to be a small man weighing 116 lb. (52.6 kg.) with pitting oedema over the sacrum and ankles. There was general bronzing of the skin, the colour being most marked over the extremities, face, and genitalia. The scalp hair was fine, soft, and lustreless. Hair was sparse on the face, absent in the axillae, and minimal in the pubic area. The testes were markedly atrophic.

The hard, smooth liver measured 5½ in. (14 cm.) in the midline and 5½ in. (14 cm.) below the costal margin in the anterior axillary line (Reidel's lobe). The spleen tip was palpable, and ascites of moderate degree with bilateral pleural effusions was present. The pulse rate was 94 and its rhythm irregular owing to auricular flutter (Fig. 1). The blood pressure was unchanged and the jugular venous pressure was high. The cardiac impulse was feeble. The heart sounds were quiet and a triple rhythm was audible at times. Chest *x*-ray examination showed a generalized increase in the size of the cardiovascular shadow. The transverse diameter of the heart measured 17 cm. and the cardiothoracic ratio was 0.66. *X*-ray examination of the spine and forearms showed generalized bony rarefaction. The serum iron was 280 μg./100 ml. E.S.R. was 50 mm. in one hour—a marked increase. Glucose-tolerance test (blood sugar per 100 ml.): fasting, 89 mg.; half an hour after ingesting 50 g. it was 200 mg.; after 1 hour 250 mg.; after 1½ hours 289 mg.; after 2 hours 211 mg.; after 2½ hours 139 mg. After 2½ hours 0.3% of glucose was found in the urine. Repeated routine urinalysis revealed no glycosuria. Liver-function tests were as follows: serum total protein, 8 g./100 ml.; serum albumin, 4.1 g./100 ml.; serum alkaline phosphatase, 12.5 K.A. units/100 ml.; serum bilirubin, 0.8 mg./100 ml.; thymol turbidity, 5 units; thymol flocculation, 1+. Serum electrolytes, including calcium and phosphate, were normal.

In view of the prognosis a systematic course of venesections was carried out. From March 6, 1955, to October 4, 1956, 500 ml. of blood a week was removed from the patient if the haemoglobin level had not fallen below 11.4 g./100 ml. (75%). At first the patient's haemopoietic response was not great enough to allow weekly venesections, but after four months this became possible. The first improvement was subjective. He felt better after 1 litre of blood was withdrawn, and in 10 weeks, when 2.5 litres of blood had been removed, he was able to walk a quarter of a mile (400 metres). Normal sinus rhythm reappeared

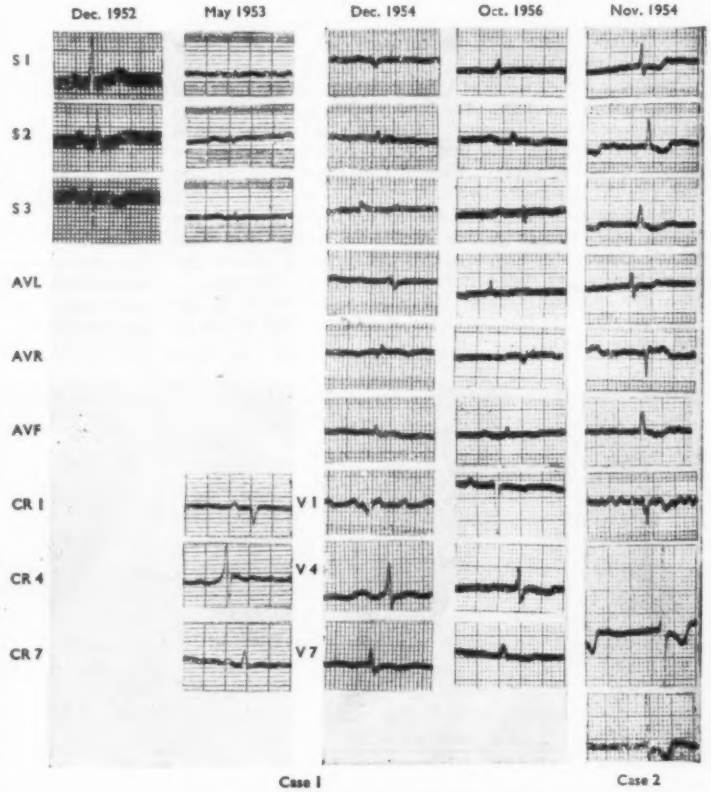


FIG. 1.—Electrocardiograms of Cases 1 and 2.

after 14 weeks, and venous congestion, pleural effusions, and ascites had disappeared. The heart size (Fig. 3) and liver size remained unchanged. After 11 months, when 18 litres of blood (9 g. of iron) had been removed, the heart size had returned to normal radiologically (Fig. 4), and exercise tolerance had increased to one mile (1.6 km.). He felt well, apart from recurrent precordial or abdominal discomfort.

Between June, 1956, and his last admission on October 10, 1956, there were increasing complaints of malaise, abdominal discomfort, and anorexia with weight loss. The urine became darker and the motions paler, while jaundice appeared at the beginning of October. At this stage he had had 33.5 litres of blood (17.75 g. of iron) removed by venesections over a period of 19 months.

On examination he was ill, the skin was lighter in colour, but pigmentation persisted and a light jaundice was superimposed. Hair distribution was unchanged, testes were unaltered clinically, and libido had not returned. In the cardiovascular system no abnormality apart from a short apical systolic murmur was found.

The liver was palpable 1 in. (2.5 cm.) below the costal margin in the mid-clavicular line, the gall-bladder was readily palpable, and the spleen tip could still be felt. The serum bilirubin was 2.8 mg./100 ml. Bilirubin was present in the urine and urobilinogen was increased. The electrocardiogram continued to show the increase in voltage noted in preceding months (Fig. 1).

At laparotomy on October 22 the gall-bladder was found to be grossly dilated and contained thin, clear bile. The pancreas was hard and enlarged. A cholecysto-jejunostomy was performed, but after operation his condition was poor and he deteriorated rapidly, passing into hepatic coma before death on the third post-operative day.

Necropsy Report

The heart weighed 320 g.; the colour was normal and both ventricular cavities were slightly dilated. There were no valvular lesions and the coronary arteries were only slightly atheromatous.

The liver, which weighed 1,980 g., was finely granular and a deep brown in colour. The fundus of the gall-bladder was anastomosed to the jejunum. A probe could not be passed along the common bile duct, but dissection revealed no stone. Chemical analysis showed that about 20 g. of iron was still present in the liver.

The pancreas was larger and firmer than normal. The spleen was enlarged (900 g.) and firm. The testes were small; the other endocrine organs were normal. There were small varicosities at the lower end of the oesophagus. A slaty-blue pigmentation of the mucous membrane of the stomach was less intense in the duodenum and absent in the rest of the gut.

Microscopy.—Heart:—The main feature was a diffuse fibrosis of the myocardium involving all chambers and the interventricular septum, with some fragmentation of the muscle fibres; no necrosis was seen. Only a scanty amount of haemosiderin was present, and most of this was seen in the fibrous tissue. The muscle cells, which were free from haemosiderin, contained a large amount of haemofuscin. *Liver*:—Diffuse hepatic fibrosis with well-marked biliary proliferation and haemosiderin, which was most pronounced at the periphery of the liver "lobules," was evident. There was less in the portal tracts and a small amount in the epithelial cells of the bile ducts. *Pancreas*:—Sections of the head showed fatty infiltration, with extensive fibrosis around the ducts and between the acini. Haemosiderin was marked in the acinar cells and to a less extent in the fibrous tissue. The islet tissue appeared to be reduced, and there were scanty haemosiderin deposits in the remaining islets. No tumour cells were seen. Testes showed atrophy of germinal epithelium.

Case 2

The patient, a colliery engine driver, was aged 58 when first admitted to the Cardiff Royal Infirmary on October 24, 1954, for investigation of a left hemianopia which had developed overnight, and which seemed to be of embolic origin. Loss of libido and increasing pigmentation had been present for 10 years and increasing breathlessness for 12 months. His general condition was good. A diffuse bronze pigmentation of the body, more pronounced on the extremities, face, and genitalia, varied in intensity from day to day. Facial, axillary, and pubic hair were present but sparse. Jugular venous congestion was present but there was no oedema. The relevant cardiovascular findings were: auricular fibrillation, pulse rate 82 and of good volume, and B.P. 150/100. The cardiac impulse was not thrusting in quality. A pansystolic murmur was audible at the apex, while the heart sounds were soft. No third heart sound was audible. Some crepitations were heard at the lung bases. The smooth, firm, non-tender liver was enlarged 4 in. (10 cm.) below the xiphisternum and 4 in. (10 cm.) below the costal margin in the mid-clavicular line. A complete left homonymous hemianopia was found together with general areflexia.

The E.C.G. (Fig. 1) showed auricular fibrillation, together with digitalis effects, and the chest *x*-ray picture revealed an overall cardiac enlargement with a transverse diameter of 16.2 cm. and a cardiothoracic ratio of 0.61. Evidence of minimal pneumoconiosis was present. Screening revealed an enlargement of both right and left ventricles with diminished ventricular pulsation. *X*-ray examination of the spine and long bones showed moderate loss of bone density and rarefaction. There were no appreciable articular changes. Total serum protein, 8 g./100 ml.; serum albumin, 3.4 g./

FIG. 2 FIG. 3 FIG. 4

FIG. 2.—Case 1. Radiograph taken before heart failure. FIG. 3. —Case 1. Radiograph during heart failure. FIG. 4.—Case 1. Radiograph after venesection.

100 ml.; alkaline phosphatase, 14 K.A. units; thymol turbidity, 7 units; thymol flocculation, 0. Glucose-tolerance test (in mg./100 ml.): fasting level, 140; half an hour after ingesting 50 g. it was 233; after 1 hour 287; after 1½ hours 243; after 2 hours 211; after 2½ hours 195. After 2½ hours 2% of sugar was present in the urine. Under normal conditions, however, the urine was glucose-free. The serum iron was 250 μg./100 ml. Skin biopsy showed the presence of haemosiderin in some of the sweat glands in the basal layer. Sternal marrow showed a marked increase of stainable iron.

The patient's condition was diagnosed as idiopathic haemochromatosis, and it was decided to treat him with digitalis and by venesection. As in the first patient, 500 ml. of blood was withdrawn at frequent intervals provided the haemoglobin levels had not fallen below 11.4 g./100 ml. From March 11, 1955, to August 6, 1956, a total amount of 37.5 litres of blood was withdrawn (18.5 g. of iron). After five months his venous congestion had disappeared, and after nine months he returned to light work underground. However, his exercise tolerance had not altered greatly. After 17 months his iron reserves were exhausted and he developed an anaemia which persisted for several weeks. His serum iron had fallen some time before. After exhaustion of his iron stores follow-up continued, and on November 28, 1958, examination revealed that he could walk up a mild gradient for ¼ mile (1.2 km.), but he was dyspnoeic after climbing 18 steps. Pigmentation was less and hair growth and impotence were unchanged. His liver was normal in size. Auricular fibrillation was still present. B.P. 155/100. An apical mid-systolic murmur was heard. Chest *x*-ray examination showed no change in the cardiac outline and size. Screening revealed a grade 3 left ventricular enlargement, a grade 2 right ventricular enlargement, and no systolic expansion of the left auricle; the cardiac pulsation was improved.

Discussion

The first patient gave a classical history of haemochromatosis with pigmentation, weakness, loss of libido, and severe congestive heart failure. Removal of the iron stores improved his general condition, his glucose tolerance, his liver, and the electrocardiogram. Most impressive of all was the rapid improvement in cardiac function, with restoration of normal cardiac size radiologically, in spite of the fact that he had more than 20 g. of iron still stored in his tissues when he died.

The second patient showed a different response to treatment, for exhaustion of his iron reserves as judged by the development of an iron-deficiency anaemia and a fall in serum iron level (Finch and Finch, 1955) produced only slight improvement. That the heart failure was due to haemochromatosis was assumed, for thorough investigation failed to reveal an alternative explanation, but the only positive support was the slight improvement in exercise tolerance and the disappearance of venous congestion following venesection. There was little doubt of the presence of haemochromatosis, for the classical features were present and venesection revealed that at least 18.5 g. of iron had been stored in his tissues.

It is believed that the basic defect in haemochromatosis is absorption of excessive amounts of iron; if this assumption is correct, the prevention of abnormal absorption or the removal of the excessive deposits is a logical form of treatment. Venesection when first introduced (Balfour *et al.*, 1942; Finch, 1949) appeared to be an excellent method of removing the iron deposits from the body and reversing the disease process.

Although much has been written since then (Davis and Laurens, 1950; Davis and Arrowsmith, 1952, 1953; Blackburn *et al.*, 1953; Warthin *et al.*, 1953; Bradford *et al.*, 1953; Houston, 1953; Peterson and Ettinger, 1953; Howard *et al.*, 1954; Fineberg, 1954; Davey *et al.*, 1954; Davis, 1955; Finch and Finch, 1955; Drew, 1955; Christensen, 1955; Kleckner *et al.*, 1955; Myerson and Carroll, 1955; Pirart and Carpent, 1955; von Kappeler, 1956; Vaisrub and Karlinsky, 1956; Althausen and Sborov, 1956; McAllen *et al.*, 1957) on the use of venesection in haemochromatosis, few cases have been described in sufficient detail to make precise comparisons. Of 34 cases, 29 have improved, subjectively or objectively, in that pigmentation has diminished, liver enlargement has receded, or insulin requirements have been less. In three cases (Warthin *et al.*, 1953; Myerson and Carroll, 1955; McAllen *et al.*, 1957) libido has returned. Venesection, however, does not cause the cirrhosis to disappear (Peterson and Ettinger, 1953), although the liver size is reduced, nor does it prevent a hepatoma developing (Bradford *et al.*, 1953; Davis, 1955). Similarly, diabetes has developed nine months after venesection has started (Christensen, 1955), and, in our case, a "benign" fibrosis of the pancreas causing bile-duct obstruction occurred after 15 months' treatment.

Of cases of heart failure in haemochromatosis treated by venesection only two other than ours have been published. One case (Christensen, 1955) was found at necropsy to be due to constrictive pericarditis, so that the lack of response was not surprising. The other case (McAllen *et al.*, 1957) had had signs of increasing cardiac decompensation for 12 months before admission to hospital. Improvement on venesection was rapid enough to allow him to return to work after two months, but radiologically his heart remained unchanged in size for over two years. Our two cases responded to a differing degree. The first patient made a remarkable improvement with eventual return of heart size to normal, while the other one showed a definite but only partial response.

Other reports (Bradford *et al.*, 1953; Davis, 1955; and McAllen *et al.*, 1957) refer to E.C.G. changes, but only three cases have been reported in detail. In one case low T waves reverted to normal, and in another the T waves improved but later became flattened again; the third case showed no change. An interesting pattern was noted in our Case 1. The standard E.C.G. leads were at first normal. After the rapid development of cardiac failure the E.C.G. became abnormal with lower voltage QRS complexes and flattened T waves. Auricular flutter occurred later, and its disappearance was one of the first responses to venesection, but the E.C.G. did not revert to its initial form even months after the cardiac silhouette became normal, nor after 17.75 g. of iron had been removed. In Case 2 the E.C.G. was abnormal before and after treatment without any improvement.

This variation in results following treatment needs to be explained, for the above brief review of published case reports shows that removal of iron deposits does not always revert or arrest this disease process.

The question of why a feeling of well-being occurs so soon after venesection has started also needs interpretation. As yet no answer has been found, but the work of Racker and Krimsky (1948) and Krimsky and Racker (1949), for example, shows that small amounts of ferrous iron cause inactivation of enzymes, including those dealing with glucose metabolism such as glyceraldehyde phosphate dehydrogenase. Mobilization

of iron by venesection would reduce the amount of iron inhibiting the enzymes and allow more efficient tissue metabolism and consequent increase of well-being. It would permit organ damage to be reversed in some cases as in Case 1.

We believe that this explanation of the improvement in haemochromatosis is a reasonable one and fits in with the facts available. What is more difficult is to explain why some cases do not respond so well and why progressive fibrosis or diabetes mellitus may develop during mobilization of iron. At present one can only suggest that a critical irreversible stage has been passed in those cases, whatever that means.

Summary

Two cases of haemochromatotic heart failure which were treated by venesection and removal of iron deposits are described. The diagnosis of haemochromatosis was made in one patient before heart failure developed, and progressive deterioration was arrested in a dramatic fashion by venesection, but death after obstructive jaundice occurred 20 months after treatment began. The second case had a similar clinical picture but failed to improve to such a degree, although the liver returned to normal size, and the patient went back to work. A brief review of the literature dealing with the results of venesection, together with an attempt to correlate the results of treatment and the mechanism of symptom formation, has been made.

While venesection remains the treatment of choice in haemochromatosis the results are not completely satisfactory.

Gratitude is expressed to Dr. G. H. Roberts, who allowed me to utilize his necropsy report. I thank Dr. Leonard Howells for his help and permission to publish the case reports, and Dr. William Phillips for his helpful criticism. The help of Miss Rumbelow, who was responsible for the electrocardiograms, Dr. Keyser and Mr. S. Nethercott, who estimated the iron contents, and Mr. Marshall, who supplied the photographs, is gratefully acknowledged.

REFERENCES

Althausen, T. L., and Sborov, V. M. (1956). In *Diseases of Liver*, edited by L. Schiff, p. 488. Pitman Med. Publ. Co., London.
Balfour, W. M., Hahn, P. F., Bale, W. F., Pommerenke, W. T., and Whipple, G. H. (1942). *J. exp. Med.*, **76**, 15.
Blackburn, C. R. B., McGuinness, A. E., and Kaldor, I. (1953). *Aust. Ann. Med.*, **2**, 202.
Bradford, J. K., Arrowsmith, W., Davis, W. D., and Findley, T. (1953). *Postgrad. Med.*, **14**, 403.
Christensen, R. (1955). *Ugeskr. Læg.*, **117**, 445.
Davey, D. A., Foxell, A. W. H., and Kempt, T. A. (1954). *Brit. med. J.*, **2**, 1511.
Davis, W. D. (1955). *Sth. med. J. (Bgham, Ala.)*, **48**, 901.
—— and Arrowsmith, W. R. (1952). *J. Lab. clin. Med.*, **39**, 526.
—— —— (1953). *Ann. intern. Med.*, **39**, 723.
—— and Laurens, H. (1950). *Sth. med. J. (Bgham, Ala.)*, **43**, 217.
Drew, W. R. M. (1955). *Trans. med. Soc. Lond.*, **71**, 38.
Finch, C. A. (1949). *J. clin. Invest.*, **28**, 780.
Finch, S. C., and Finch, C. A. (1955). *Medicine (Baltimore)*, **34**, 381.
Fineberg, S. K. (1954). *N.Y. St. J. Med.*, **54**, 1915.
Houston, J. C. (1953). *Lancet*, **1**, 766.
Howard, R. B., Balfour, W. M., and Cullen, R. (1954). *J. Lab. clin. Med.*, **43**, 848.
Kappeler, R. von (1956). *Schweiz. med. Wschr.*, **86**, 477.
Kleckner, M. S., Kark, R. M., Baker, L. A., Chapman, A. Z., Kaplan, E., and Moore, T. J. (1955). *J. Amer. med. Ass.*, **157**, 1471.
Krimsky, I., and Racker, E. (1949). *J. biol. Chem.*, **179**, 903.
McAllen, P. M., Coghill, N. E., and Lubran, M. (1957). *Quart. J. Med.*, **26**, 251.
Myerson, R. M., and Carroll, I. N (1955). *A.M.A. Arch. intern. Med.*, **95**, 349.
Peterson, R. E., and Ettinger, R. H. (1953). *Amer. J. Med.*, **15**, 518.
Pirat, J., and Carpent, G. (1955). *Acta gastro-ent. belg.*, **18**, 7.
Racker, E., and Krimsky, I. (1948). *J. biol. Chem.*, **173**, 519.
Vainrub, S., and Karlinsky, W. (1956). *Canad. Serv. med. J.*, **12**, 81.
Warthin, T. A., Peterson, E. W., and Barr, J. H. (1953). *Ann. intern. Med.*, **38**, 1066.

INCREASED THYROID FUNCTION IN HAEMOCHROMATOSIS

BY

R. S. WILLIAMS,* M.B., M.R.C.P.
Late Captain, R.A.M.C.
From the Queen Alexandra Military Hospital, Millbank

In at least 90% of cases of haemochromatosis there is deposition of iron in the thyroid, often associated with considerable fibrosis (Sheldon, 1935), but, in spite of this, thyroid function is rarely disturbed.

Occasional cases of hypothyroidism have, however, been reported. In 1935 Darnall described a case of haemochromatosis showing some clinical features of hypothyroidism which he regarded as secondary to pituitary deficiency. Two cases were reported by McAllen *et al.* (1957). In one which was grossly myxoedematous the radio-iodine test was unchanged after a course of thyrotrophic hormone, indicating a primary failure of the thyroid gland. The other, though not clinically hypothyroid, showed diminished thyroid function with the radio-iodine test, but on repeating the test after a course of thyrotrophic hormone there was a hyperthyroid response, showing that most of the depression of thyroid function was due to anterior pituitary failure.

The occurrence of increased thyroid function is even more remarkable. Althausen and Kerr (1927, 1933), in describing the various endocrine disturbances in haemochromatosis, noted three cases with a raised basal metabolic rate. One of these had suggestive signs of thyrotoxicosis with a goitre, slight exophthalmos, and lid lag, although examination of the thyroid after its removal showed no histological evidence of toxicity. There were no clinical signs of hyperthyroidism in the other two cases, but one of them later came to necropsy, and on microscopy the thyroid showed definite though mild hyperplasia together with many haemosiderin granules in the acinar cells. In explanation of these findings those authors suggested that these granules might act as minute foreign bodies and stimulate the secreting cells to increased activity.

In the following case of haemochromatosis the presenting features were those of thyrotoxicosis.

Case Report

In January, 1957, a 35-year-old sergeant noticed for the first time that his ankles were swelling at the end of the day, and that a brown pigmentation was present over the front of his legs. During the next three months he became increasingly nervous, sweated easily, and despite a good appetite lost over a stone (6.4 kg.) in weight. Later he became aware of an irregular thumping of his heart, and shortly before his admission to Queen Alexandra Military Hospital on March 15 he experienced several attacks of paroxysmal nocturnal dyspnoea. He gave a history of recurrent attacks of malaria between 1943 and 1950. There was no relevant family history.

On admission he was obviously thyrotoxic, with a hot sweaty skin, marked exophthalmos, and a fine tremor of the outstretched hands. The thyroid was diffusely enlarged, with a systolic bruit over the right lobe. Pretibial myxoedema was present and in addition there was an uneven brown pigmentation of the skin over the front of the legs and dorsum of the feet. The pulse was rapid and irregular and the blood pressure 160/80 mm. Hg. The jugular venous pressure was normal and there were no murmurs. A tender liver edge was palpable two fingerbreadths below the

*Now at the Department of Medicine, Postgraduate Medical School, London, W.12.

costal margin and a large spleen extended to four finger-breadths. There was no shifting dullness. The testes were of normal size, and pubic and axillary hair was present.

Investigations.—Haemoglobin, 15 g. per 100 ml.; white-cell count, 3,500 per c.mm., with a normal differential count; serum cholesterol, 130 mg. per 100 ml.; serum proteins, 6 g. per 100 ml. (albumin 3.2 g., globulin 2.8 g.); electrophoretic pattern normal (γ-globulin 1.28 g.). Liver-function tests: serum bilirubin 1 mg. per 100 ml., thymol turbidity 5 units, alkaline phosphatase 7.5 units, bromsulphthalein test 1% retention at 45 minutes. Barium swallow—no oesophageal varices seen. There was slight glycosuria. Glucose-tolerance test showed a "lag" type curve with a fasting blood-sugar level of 105 mg. per 100 ml. rising to a peak of 238 mg. and falling to a level of 96 mg. at two hours. The electrocardiogram confirmed the presence of auricular fibrillation, and the basal metabolic rate was +28%.

Progress and Treatment

The initial diagnosis was thyrotoxicosis and thyrotoxic heart disease, the hepato-splenomegaly being attributed to a latent cirrhosis, although there was no history of alcoholism or hepatitis. Two days after admission treatment was started with methylthiouracil, 100 mg. t.d.s., and L-thyroxine, 0.1 mg. daily. During the next few weeks his general condition improved, but at the beginning of April he complained of persistent right-sided abdominal pain and increasing abdominal distension. The size of the liver and spleen was unchanged, but the abdominal girth had increased by 3 in. (7.5 cm.) and definite shifting dullness was present. Liver-function tests on April 18 showed an increase in thymol turbidity to 10 units, with normal serum bilirubin (0.4 mg. per 100 ml.) and alkaline phosphatase (9.5 units) levels.

At this stage carbimazole ("neo-mercazole"), 10 mg. t.d.s., was substituted for thiouracil as it was thought that this might be responsible for the deterioration in hepatic function. During the next week he improved, and on May 9 there was a spontaneous reversion to sinus rhythm. His abdominal girth decreased and the signs of ascites disappeared. Liver-function tests on May 20, however, showed a thymol turbidity of 12 units, with a striking increase in γ-globulin to 2.55 g. per 100 ml. which over the next month increased to a maximum of 2.82 g. per 100 ml. A further complication arose on May 27, when he developed an unexplained purpuric eruption over both legs. A skin biopsy from this area showed granules of haemosiderin scattered through the corium, especially around the sweat glands, but a further biopsy from the trunk was normal. The rash cleared and he steadily improved, the dose of carbimazole being gradually increased to 55 mg. daily.

By the beginning of August he was clinically euthyroid and after a course of Lugol's iodine a partial thyroidectomy was performed, three-quarters of each lobe being removed. Histological examination of the gland showed the picture of a partially treated toxic goitre with large colloid-filled acini in some areas but in other parts considerable glandular activity with sheets of acinar cells and colloid resorption.

On return from sick leave a month later he was clearly toxic again, with a rapid pulse and hot sweaty skin. The B.M.R. was +31%. He was restarted on carbimazole, 10 mg. t.d.s., with rapid disappearance of the signs of toxicity. The hepato-splenomegaly and abnormal liver-function findings were unchanged, the liver remaining very tender to palpation. On October 9 a liver biopsy showed a portal cirrhosis with large amounts of iron-staining pigment in the periportal areas and in the parenchymal liver cells (Fig. 1). The serum iron level was then estimated and found to be high (228 μg. per 100 ml.) and the iron-binding capacity fully saturated. Finally, staining of the resected thyroid for iron showed large numbers of haemosiderin granules, mainly in the acinar cells lining the colloid spaces (Fig. 2).

With the diagnosis of haemochromatosis firmly established the patient was started on a long-term programme of repeated venesections. A pint (570 ml.) of blood was withdrawn daily for the first 10 days, weekly for a month, and then subsequently once a fortnight. There was an initial fall in haemoglobin to 9 g. per 100 ml.; it then rose again despite continued venesections and has remained between 13 and 14 g. per 100 ml. Six weeks after starting the venesections the electrophoretic pattern of his serum proteins had returned to normal (γ-globulin 1.36 g. per 100 ml.) although flocculation tests were still strongly positive.

When seen in July, 1958, eight months after venesections were started, he was well and had returned to work. The liver was no longer palpable and the pigmentation of the legs much less pronounced. The flocculation tests were normal, the thymol turbidity being 2 units.

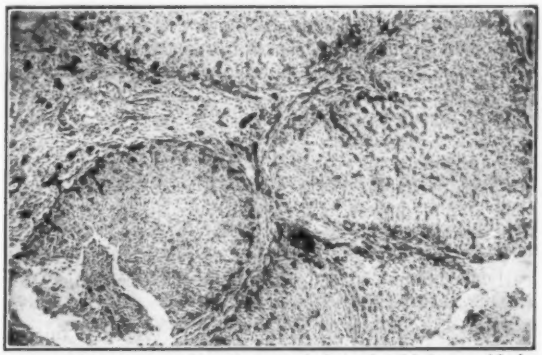


FIG. 1.—Liver biopsy showed a portal cirrhosis with haemosiderin granules in the liver cells and in the periportal areas.

FIG. 2.—Section of resected thyroid showing haemosiderin granules in the acinar cells lining the colloid spaces. (Perles stain.)

Discussion

There can be no doubt about the diagnosis of haemochromatosis in this case. The liver biopsy showed the classical pigmentary cirrhosis, and the combination of a raised serum iron level with a fully saturated iron-binding capacity is diagnostic (Houston and Thompson, 1952, 1953). The pigmentation was unusual in being confined to the legs, there being no abnormal pigmentation of the face, forearms, or genitalia, which are the sites usually affected in haemochromatosis (Sheldon, 1935). Owing to the presence of purpura no reliance could be placed upon the finding of haemosiderin deposits in the biopsy specimen of the skin taken from the leg, although it is interesting to note that these deposits were situated in the deeper layers of the skin around the sweat glands, which is the characteristic site for iron deposition in haemochromatosis. It has been

said that deposits of haemosiderin resulting from such vascular disturbances become unduly prominent in haemochromatosis as the excessive body iron limits their reabsorption (Finch and Finch, 1955). One of the striking clinical features was the complaint of persistent right-sided upper abdominal pain with marked tenderness of the liver on palpation. Abdominal pain is in fact common in haemochromatosis, occurring in 37% of the patients in one series (Marble and Bailey, 1951), and is thought to be due to distension of the liver capsule by intrahepatic iron deposits.

The case presented several unusual features. The spleen was much enlarged, although this may have been related to the recurrent attacks of malaria in the past. Glycosuria was present, but it was clearly due to the "lag" type of impaired glucose tolerance which is often seen in thyrotoxicosis and attributed to rapid intestinal absorption of glucose. Finally, there was no evidence of hypogonadism, which is one of the more constant features of haemochromatosis. It has been suggested that hypogonadism with testicular atrophy in this condition is due to damage to the anterior lobe of the pituitary by deposits of haemosiderin, which may be particularly marked in the basophil cells (Sheldon, 1935; Althausen *et al.*, 1951).

Another explanation is that primary testicular failure occurs as the result of deposition of iron in the testis; but this is never very marked, and the deposits are found in the walls of the blood vessels and only rarely in the germinal epithelium. In ordinary portal cirrhosis hypogonadism is attributed to failure of the damaged liver to inactive oestrogens, but this is much less likely to be true for haemochromatosis, in which there is less disturbance of liver function, at least until the later stages. If the pituitary origin of the gonadal failure is accepted, then its absence in this case is good evidence that the pituitary was not significantly damaged, as deficient gonadotrophin formation is usually the first sign of anterior pituitary failure. This may be relevant to the subsequent development of thyrotoxicosis, for, although the exact role of the pituitary in the aetiology of thyrotoxicosis is not known, both pretibial myxoedema and exophthalmos are usually attributed to pituitary overactivity, and the initial stimulus to the thyroid gland may well be excess formation of thyrotrophic hormone.

Whether the haemochromatosis was responsible in any way for the development of thyrotoxicosis is not known, but, even if unrelated, the presence of impaired hepatic function due to deposition of iron in the liver may well have aggravated the thyroid toxicity. Thyroxine is excreted by the liver into the bile mainly in the form of a glucuronide (Myant, 1956), and increased serum protein-bound iodine levels have been reported in acute hepatitis (Kydd and Man, 1951), so that it is not surprising that liver disease is said to aggravate thyrotoxicosis.

Since Paul in 1865 described a case of cirrhosis of the liver in a woman dying of thyrotoxicosis there have been numerous reports concerning abnormal hepatic function and pathological changes in the liver in thyrotoxicosis (Cameron and Karunaratne, 1935; Allison, 1949; Movitt *et al.*, 1953). Experimentally, liver glycogen is depleted by feeding thyroid to animals and both toxic and dietary liver injury are potentiated. Himsworth (1947) suggested that liver damage in this disorder was due to a relative deficiency of such factors as cystine, methionine, and tocopherol, and, in support of this, Allison (1949) found a relationship between the degree of impairment of liver function and the degree of weight loss in thyrotoxicosis prior to treatment. It has also been shown (Myers *et al.*, 1950) that the hepatic blood flow in thyrotoxicosis is little if at all increased despite the increased cardiac output, and as the oxygen requirements of the liver are increased it is very likely that the centrilobular areas which receive their blood supply last may suffer from anoxia, with resulting necrosis. Whatever the mechanism of liver damage in thyrotoxicosis, it seems reasonable to assume that the onset of thyrotoxicosis would be a further insult to a liver already damaged by haemochromatosis. This may well have been the explanation of the deterioration in hepatic function which occurred after admission to hospital before the thyroid toxicity was controlled, although the possibility that this was a toxic reaction to thiouracil cannot be excluded.

The treatment of haemochromatosis by repeated venesections is now well established (Finch *et al.*, 1950; Davis and Arrowsmith, 1952; McAllen *et al.*, 1957) although the long-term results are not known. Certainly there has been a marked clinical improvement in this patient, with decrease in size of the liver and improvement in hepatic function. It is hoped that by reducing the iron stores to normal further progress of the disease will be prevented.

Summary

Attention is drawn to the surprising rarity of disturbance of thyroid function in haemochromatosis, and a case is described which presented with thyrotoxicosis. It is suggested that a vicious circle occurred in which the thyrotoxicosis caused further damage to a liver already the site of extensive iron deposition and fibrosis. This impairment of hepatic function in its turn aggravated the thyroid toxicity, possibly as a result of a failure of detoxication of thyroid hormone.

I thank Lieutenant-Colonel J. P. Baird and Lieutenant-Colonel R. M. Johnstone for their guidance and encouragement. I am indebted to Dr. I. M. P. Dawson and Lieutenant-Colonel P. D. Stewart for the histological reports on the liver biopsy and thyroid.

References

Allison, A. (1949). *Glasg. med. J.*, **30**, 417.
Althausen, T. L., Doig, R. K., Weiden, S., Motteram, R., Turner, C. N., and Moore, A. (1951). *A.M.A. Arch. intern. Med.*, **88**, 553.
—— and Kerr, W. J. (1927). *Endocrinology*, **11**, 377.
—— —— (1933). Ibid., **17**, 621.
Cameron, G. R., and Karunaratne, W. A. E. (1935). *J. Path. Bact.*, **41**, 267.
Darnall, J. R. (1935). *Ann. intern. Med.*, **8**, 1121.
Davis, W. D., and Arrowsmith, W. R. (1952). *J. Lab. clin. Med.*, **39**, 526.
—— —— (1953). *Ann. intern. Med.*, **39**, 723.
Finch, S., and Finch, C. A. (1955). *Medicine (Baltimore)*, **34**, 381.
—— Haskins, D., and Finch, C. A. (1950). *J. clin. Invest.*, **29**, 1078.
Himsworth, H. P. (1947). *Lectures on the Liver and its Diseases*. Blackwell Scientific Publications, Oxford.
Houston, J. C., and Thompson, R. H. S. (1952). *Quart. J. Med.*, **21**, 215.
—— —— (1953). *Guy's Hosp. Rep.*, **102**, 355.
Kydd, D. M., and Man, E. B. (1951). *J. clin. Invest.*, **30**, 874.
McAllen, P. M., Coghill, N. F., and Lubran, M. (1957). *Quart J. Med.*, **26**, 251.
Marble, A., and Bailey, C. C. (1951). *Amer. J. Med.*, **11**, 590.
Movitt, E. R., Gerstl, B., and Davis, A. E. (1953). *A.M.A. Arch. intern. Med.*, **91**, 729.
Myant, N. B. (1956). *Clin. Sci.*, **15**, 551.
Myers, J. D., Brannon, E. S., and Holland, B. C. (1950). *J. clin. Invest.*, **29**, 1069.
Paul (1865). *Berl. klin. Wschr.*, **2**, 277.
Sheldon, J. H. (1935). *Haemochromatosis*. Oxford Univ. Press, London.

TREATMENT OF CARDIAC SHOCK BY METARAMINOL

BY

E. M. M. BESTERMAN, M.A., M.D., M.R.C.P.
Senior Medical Registrar, the Middlesex Hospital, London

An 80% mortality has been reported in shock following acute cardiac infarction (Hellerstein *et al.*, 1952; Griffith *et al.*, 1954). However, this figure is probably an underestimate, as it is based on hospital experience alone. The early use of pressors has been advocated by Griffith *et al.* (1954): in a series of cases treated for shock within three hours of its onset only 13% died. Noradrenaline infusions have reduced the overall mortality to between 40% and 50% (Moyer *et al.*, 1953; Sampson and Zipser, 1954; Garai and Smith, 1958).

However satisfactory noradrenaline may be in hospital practice, the use of a drip in a patient's home presents many difficulties, and this drug is rarely used in domiciliary treatment of shock. This complication may therefore persist for several hours, with a consequently poorer prognosis, before the patient reaches hospital. Moreover, in some cases the shock is too severe to allow removal to hospital. The immediate requirement for such patients is a drug similar to noradrenaline, yet possible to administer by intravenous, intramuscular, or subcutaneous injections. Such a substance might be used either for continued therapy at home or to counter shock temporarily to allow transfer to a hospital.

Noradrenaline has been shown to increase the contractile force of the heart, increase coronary flow, and raise the peripheral vascular resistance without inducing arrhythmias or tachycardia (Burn and Hutcheon, 1949; Gazes *et al.*, 1953; Denison *et al.*, 1956). Other pressors such as phenylephrine work by a purely peripheral action on the systemic resistance and have been found less effective in the treatment of cardiac shock. This difference is attributed to the direct myocardial action of noradrenaline (Gazes *et al.*, 1953).

Mephentermine sulphate has been used successfully in the treatment of cardiac shock by Brofman *et al.* (1952), Hellerstein *et al.* (1952), and Garai and Smith (1958). This drug may be given by injection or by drip, and causes a rise in systemic pressure and an increased coronary blood flow. Recent experimental studies in dogs have shown that the pressor effects of mephentermine are due to its central action rather than to peripheral vasoconstriction (Welch *et al.*, 1958). Clinically the only drawback to this drug is the occasional development of tachyphylaxis: an increasing refractoriness to repeated injections necessitating larger doses of mephentermine in order to achieve a satisfactory pressor response.

Metaraminol bitartrate ("aramine"; laevo-1 (hydroxyphenyl) - 2 - amino - 1 - propanol hydrogen d - tartrate) seems to possess the properties of direct action on the heart as well as on the peripheral resistance. It may be administered by repeated injections without the development of tachyphylaxis. In experimental cardiac ischaemia Sarnoff *et al.* (1954) produced a fall of arterial pressure, of cardiac output, and of ventricular stroke work, with a rise of left atrial pressure. Subsequent intravenous metaraminol returned these values to near normal levels and increased coronary flow. This and other experiments indicated that metaraminol produced a sustained increase of myocardial contractility without requiring increased coronary flow per unit of ventricular work. This central action, together with the peripheral effects, achieve the most desirable results—namely, increased arterial pressure and cardiac output at a low atrial pressure. No arrhythmias or tachycardia were observed.

In hypotensive human subjects metaraminol caused an increased renal and cerebral blood flow (Moyer and Morris, 1954; Moyer *et al.*, 1954). In the United States this drug has been used for the treatment of shock in a variety of conditions, both medical and surgical, and also for maintaining blood pressure during spinal anaesthesia (Poe, 1954; Weil, 1955; Moyer and Beazley, 1955). Stechel *et al.* (1956) included 16 cases of cardiac shock in a series of 250 patients with varied types of shock treated by metaraminol infusions. Only 5 of these 16 patients survived. However, no report has yet appeared on the use of this drug by intermittent injection in cardiac shock.

Indications.—Some hypotension is common in cardiac infarction, but "shock," justifying therapy, was regarded as present only when the systolic pressure fell to 85 mm. Hg. Less severe hypotension reduces the work of the heart, and attempts to restore the pressure to normal levels may impose an excessive load on the damaged myocardium. For this reason it has been our practice to initiate pressor therapy only when the systolic pressure has fallen to 85 mm. Hg or less. Furthermore, when using pressors we have tried to avoid raising the systolic pressure higher than 110 mm. Hg.

Treatment

Twelve patients have been treated with metaraminol by intermittent injection. Five of them also received other pressors: mephentermine in four, noradrenaline infusions in two. Details of these cases are shown in Table I.

The initial intravenous dose of metaraminol should not exceed 1.25 mg. Often this proves inadequate and may need to be repeated. 2.5 mg. may be given by intramuscular or subcutaneous routes and subsequent doses determined by the pressor response. However, we have never used more than 5 mg. in one injection. The pressor effects of intravenous metaraminol appear within three minutes and persist for 10 to 30 minutes. The response to intramuscular injection occurs within 10 to 20 minutes and lasts one to three hours, whereas the pressor action appears 30 to 45 minutes after subcutaneous injection and persists for two to four hours. In severe shock absorption from subcutaneous injections is poor, and intramuscular injections were used after the initial one or more intravenous injections.

Mephentermine was used first in four patients. In two cases an immediate pressor response occurred, but subsequent injections proved ineffective. Thereafter noradrenaline and metaraminol were used in one and metaraminol alone in the second case: in both a pressor response was obtained, but both patients died later. The other two patients showed no pressor response to intramuscular mephentermine: intramuscular metaraminol was then used with success and eventual recovery.

Noradrenaline infusions were used only twice. In one case it was employed after mephentermine had

proved ineffective and the pressure was maintained for 40 hours (Case 1, Table II). During the period of pressor response intermittent intravenous metaraminol was substituted for the noradrenaline, a total of 1.3 mg. being required over a period of 45 minutes to maintain the pressure at the same level as that obtained with noradrenaline, 20–24μg./minute. In the other patient profound shock was present, refractory to both noradrenaline and metaraminol. Metaraminol was used alone in the remaining seven patients, three of whom died.

Results of Metaraminol Therapy (Table II)

Six Fatal Cases.—Case 1 was treated with noradrenaline; metaraminol was used over 45 minutes to demonstrate that it could substitute an equally effective pressor action. In three of the remaining five fatal cases shock was present before admission to hospital and had lasted four hours or longer. The other two patients were treated within half an hour of the onset of shock, which occurred in hospital. In Cases 3 and 4 the blood pressure was sustained until death. Two other patients (Cases 2 and 6) exhibited initial pressor responses but died in a state of terminal irreversible hypotension. Only one patient (Case 5) was absolutely refractory to treatment from the onset of shock. All these five deaths occurred within six hours of the onset of shock. Acute left ventricular failure was present at some stage in four cases and congestive heart failure had appeared in three of them. All were promptly digitalized with lanatoside C. Arrhythmias were present in two: atrial fibrillation and atrial flutter. The ventricular rates were controlled by lanatoside C. Permission for necropsy was obtained in only one case (No. 4): widespread infarction was found involving the left ventricle and the entire septum.

Six Survivors.—All the surviving cases developed shock after admission to hospital and were therefore treated within 15 to 30 minutes of the onset. With one exception pressor therapy had to be maintained for a minimum of 12 hours: three required metaraminol for 24 to 36 hours, and one for nearly six days. The average hourly dose of metaraminol was found to be 1.3 mg. in three cases and 0.3–0.9 mg. in the remaining cases. Congestive failure was present in three of these survivors, atrial fibrillation occurred in one, and transient complete heart-block in another.

Discussion

When cardiac shock is due to extensive infarction, pressor therapy is bound to be useless. However, treatment has reduced the mortality of this complication to 50%. The value of immediate therapy has already been noted by Griffith *et al.* (1954), and in the present small series there was a 25% mortality in those cases treated promptly as opposed to a 100% mortality in the four with shock of some hours' duration before treatment. Once pressors are given, some encouragement

TABLE I.—*Clinical Features of 12 Patients (not numbered chronologically)*

No.	Sex	Age	Duration of Previous Angina Pectoris	Site of Present Infarction	Onset of Shock after Infarction	Arrhythmia	Failure	Previous B.P.	B.P. at Start of Treatment	B.P. after Recovery	Duration of Shock before Death	Result
1	M	64	2 years	Ant.	4 hours	0	0	140/70	75/45		3 days	Died
2	M	49	2 ,,	Ant.-sept.	Immediate	0	+	180/110	60/40		6 hours	,,
3	M	54	2 ,,	Post.	7 hours	A. fib.	+	120/80	85/50		1 hour	,,
4	F	73	None	,,	Immediate	0	+	Unknown	85/60		6 hours	,,
5	M	60	5 years	Ant.-sept.	11 hours	0	0	170/85	Unobtainable		2 ,,	,,
6	M	48	4 ,,	Post.	Immediate	A. flutter L.B.B.B.	+	190/110	70/50		6 ,,	,,
7	M	58	5 ,,	Ant.	12 hours	R.B.B.B.	+	150/90	80/55	125/85		Survived
8	M	56	None	,,	18 ,,	0	0	Unknown	75/55	90/60		,,
9	F	63	1 year	,,	2 days	0	+	140/100	85/60	110/80		,,
10	F	58	None	Post.	12 hours	C.H.B.	+	Unknown	70/40	170/95		,,
11	F	76	7 years	Ant.	3 days	A. fib.	0	295/135	80/60	140/90		,,
12	M	60	4 months	Post.-lat.	24 hours	0	0	Unknown	80/55	140/80		,,

TABLE II.—*Details of Pressor Therapy*

No.	Duration of Shock before Treatment (Hours)	B.P. at Time of Treatment	Average Maintained B.P.	Mephentermine		Noradrenaline		Metaraminol		Duration of Pressor Therapy (Hours)	B.P. Immediately before Death	B.P. 24 Hours after Stopping Treatment	Average Dose of Metaraminol Required (mg/hr.)
				Dosage mg.	Duration of Response		Duration of Response	Dosage mg.	Duration of Response				
1	4	75/45	105/60	15 I.V. 15 I.V. 15 I.M.	1 hour None	+	40 hours	1·3 I.V. in 45 mins.	48 mins.	48	Unobtainable for 5 hours		2·0
2	4+	60/40	80/55					5 I.M. 2·5 S.C.	2½ hrs.	2½	60/40		3·0
3	½	85/50	100/70					2·5 S.C.	1 hour	1	100/70		2·5
4	6+	85/60	100/80					2·5 I.M.	4 hrs.	4	100/80		0·6
5	½	Unobtainable				+	None	7·5 I.M.	None	2	Unobtainable		
6	4	60/40	70/40	75 in ½ hr.	½ hr.			2·5 I.M.	½ hr.	2	65/40		5·0
7	½	80/55	90/60					182·5 I.V., I.M. (56 doses)	137 hrs.			100/70	1·3
8	½	70/55	95/65					10 I.M.	3 hrs.			110/70	1·4
9	½	85/60	105/70					22·5 I.M.	20 ,,				
10	½	70/40	110/70	30 I.M.	None			7·5 I.M. 7·5 S.C. 5 I.V. 20 I.M. 12·5 S.C.	26 ,, 30 ,,			100/70 115/70	0·6 1·3
11	½	80/60	100/75					0·5 I.V. 2 I.M. 5 S.C.	24 ,,			140/100	0·3
12	½	80/55	90/60	15 I.M.	None			12·5 I.M.	14 ,,			100/70	0·9

can be felt if the blood pressure is sustained for longer than four hours. Only one death in this series followed a prolonged pressor response.

Intermittent injection of metaraminol has proved successful in maintaining the blood pressure for several days if necessary. Unnecessarily frequent injections of small doses were used initially in order to avoid the hazard of a severe pressor response. With more experience, fewer doses of larger amounts have been used. The frequency of injection has been determined by repeated blood-pressure estimations at 10- or 15-minute intervals, metaraminol being given whenever the systolic pressure fell to 85 mm. Hg or less.

No tachyphylaxis has occurred with this drug as was met with in two patients receiving mephentermine.

In a further two cases metaraminol proved effective when mephentermine had failed to raise the pressure. This study was not intended as a comparison of the pressor effects of these two drugs, but solely to assess the value of metaraminol. No doubt the use of increasingly large doses of mephentermine would have achieved a pressor response in these patients. However, the repeated efficiency of identical doses of metaraminol has proved of great value.

It would appear that metaraminol is the drug of choice for intermittent parenteral use in cardiac shock and should therefore be of particular benefit in the domiciliary treatment of this condition.

Coincident heart failure or arrhythmias should be treated immediately: four of the survivors had suffered from one or more of these additional complications.

No undesirable side-effects have accompanied the use of metaraminol.

Summary

Results are presented of the use of metaraminol in 12 patients suffering from cardiac shock. This drug has a similar action to that of noradrenaline but has the advantage that it may be given by subcutaneous, intramuscular, or intravenous injection. For this reason it should prove of value in the domiciliary treatment of cardiac shock.

The 50% mortality in this series included all the patients with shock of four or more hours' duration. This observation is in accord with the experience of others, and demonstrates the need for early treatment of this complication of cardiac infarction.

The patients treated in this study were under the care of Drs. D. Evan Bedford and Walter Somerville. I am most grateful for the opportunity to undertake this work, and also for their encouragement and helpful criticism. I am grateful to the successive house-physicians who have assisted me so patiently. The metaraminol was kindly supplied by Merck Sharp and Dohme Ltd.

REFERENCES

Brofman, B. L., Hellerstein, H. K., and Caskey, W. H. (1952). *Amer. Heart J.*, **44**, 396.
Burn, J. H., and Hutcheon, D. E. (1949). *Brit. J. Pharmacol.*, **4**, 373.
Denison, A. B., Bardhanabaedya, S., and Green, H. D. (1956). *Circulat. Res.*, **4**, 653.
Garai, O., and Smith, K. S. (1958). *Brit. med. J.*, **1**, 247.
Gazes, P. C., Goldberg, L. I., and Darby, T. D. (1953). *Circulation*, **8**, 883.
Griffith, G. C., Wallace, W. B., Cochran, B., Nerlich, W. E., and Frasher, W. G. (1954). Ibid., **9**, 527.
Hellerstein, H. K., Brofman, B. L., and Caskey, W. H. (1952). *Amer. Heart J.*, **44**, 407.
Moyer, J. H., and Beazley, H. L. (1955). Ibid., **50**, 136.
—— and Morris, G. (1954). *Postgrad. Med.*, **16**, 287.
—— —— Snyder, H., and Smith, C. P. (1954). *Circulation*, **10**, 265.
Moyer, J. H., Skelton, J. M., and Mills, L. C. (1953). *Amer. J. Med.*, **15**, 330.
Poe, M. F. (1954). *Anesthesiology*, **15**, 547.
Sampson, J. J., and Zipser, A. (1954). *Circulation*, **9**, 38.
Sarnoff, S. J., Case, R. B., Berglund, E., and Sarnoff, L. C. (1954). Ibid., **10**, 84.
Stechel, G. H., Fis..man, S. I., Schwartz, G., Turkowitz, H., Madonia, P. F., and Fankhauser, A. (1956). Ibid., **13**, 834.
Weil, M. H. (1955). *Amer. J. med. Sci.*, **230**, 357.
Welch, G. H., Braunwald, E., Case, R. B., and Sarnoff, S. J. (1958). *Amer. J. Med.*, **24**, 871.

A COMPARISON OF THE RESPONSES OF 100 INFANTS TO PRIMARY POLIOMYELITIS IMMUNIZATION WITH TWO AND WITH THREE DOSES OF VACCINE

BY

F. T. PERKINS, M.Sc., Ph.D.

RISHA YETTS, B.Sc.

From the Biological Standards Control Laboratory, Medical Research Council Laboratories, London, N.W.3

AND

WILFRID GAISFORD, M.D., M.Sc., F.R.C.P.

Director of the Department of Child Health, University of Manchester

In previous investigations (Perkins, Yetts, and Gaisford, 1958, 1959) it was shown that in only a small proportion of infants under the age of 10 weeks could a satisfactory basal immunity be established by the injection of two doses of poliomyelitis vaccine. This was evident not only from the responses to primary immunization but also from those obtained when a booster dose was given 10 to 12 months later. It was concluded that two factors were responsible for the poor responses—namely, the inhibiting effect of maternally transmitted antibody and the necessity for highly potent antigens in early infancy. In view of these findings, two further studies were made. The first, with 1-week-old infants, was designed to determine whether the inhibiting action of maternal antibody could be overcome by increasing the number and size of the doses. The second study, with 16-weeks-old infants, was made in order to determine whether infants of this age had reached a stage at which their immunological activity would overcome the inhibiting effect of passively acquired antibodies and also to investigate whether a more substantial basal immunity could be established by three doses than by two. By analogy with pertussis and diphtheria immunization in infants it might be expected that poliomyelitis would require a similar course, and that, if the vaccine was comparable in antigenicity to pertussis vaccine and diphtheria toxoid, results might be similar.

Procedures

One-week-old Infants.—In this group there were 45 infants, of whom 36 received three doses and 9 received only two. The vaccine was given at intervals of four weeks, and all infants were 1 week old at the time they received the first injection. Each dose was 2 ml., which was double the normal, and was given by injecting 1 ml.

into each buttock. The total volume was thus 4 ml. for those who received two doses and 6 ml. for those who received three. Serum was collected from the cord blood of all infants and served as the pre-immunization sample. Post-immunization serum samples were taken (1) four weeks after the second dose, which was at the time of the third dose, and (2) 14 to 21 days later. Samples were obtained after both the second and third doses from 27 infants, after the second dose only from 9, and after the third dose only from the remaining 9.

Sixteen-weeks-old Infants.—55 infants were given three doses of vaccine intramuscularly, each of 1 ml., spaced at intervals of four weeks. All were 15 to 17 weeks of age at the time they received the first dose. From all infants serum samples were collected from the cord blood, and pre-immunization samples were taken on the day the first dose of vaccine was given. Post-immunization samples were taken from 43 after both the second and third doses, from 6 after the second dose, and from the remaining 6 after the third dose only. As with the 1-week-old infants, samples were taken four weeks after the second dose and 14 to 21 days after the third.

Vaccine.—Two vaccines were used in each group. One of these, Glaxo batch 24, was prepared from Brunenders (type 1), MEF-1 (type 2), and Saukett (type 3) strains, whilst the other, Connaught batch 75, differed from the British vaccine in the type 1 component, for which the Mahoney strain was used. The two batches, which showed similar antigenic activity in monkeys, were distributed equally between the two age groups, and, because the responses to both vaccines were similar, the results from each group have been combined.

Titration of Sera.—Sera were titrated by the method used in the previous investigations. For each infant all serum samples were titrated in parallel in the same test in order that a valid comparison of antibody levels could be made. All titres are given as the dilution of serum in the serum–virus mixtures before the addition to cell cultures.

Antibody Levels in Cord Blood and Loss of Maternally Transmitted Antibody in Infants

Table I gives the distribution of antibodies in the cord sera of 100 of the infants. The group was very similar to the one in the previous study (Perkins *et al.*, 1958) in that a large proportion (59) had antibodies to all three types and only five had no antibodies to any of the types. There was considerable variation in the antibody levels, which ranged from 8 to 16,384 for each type. The number of infants with no detectable antibody to one particular type was similar, being 23 for type 1, 17 for type 2, and 24 for type 3.

TABLE I.—*Distribution of Poliomyelitis Antibodies in the Cord Sera of 100 Infants*

No. of Sera	No. of Sera with Antibodies to:			
	No Type	One Type Only	Two Types Only	Three Types
100	5	16	20	59

The loss of maternal antibody in the 16-weeks-old infants is shown in Table II, in which the mean titre of the sera obtained at the time of giving the first dose of vaccine is compared with that of the cord sera. The loss of maternal antibodies was similar for each type, and such a decline is consistent with the findings of our earlier report that the maternal antibody level was halved every 21 days.

TABLE II.—*Loss of Maternal Antibody in 16-Weeks-Old Infants*

No. of Sera	Virus Type	Geometric Mean Antibody Titre of Sera of		Loss of Antibody
		Cord	Infant	
38	1	485	20	96%
41	2	625	24	96%
38	3	135	7	95%

Response of 1-week-old Infants to Two and Three Doses of Vaccine

The antibody responses of the 1-week-old infants to two and three doses of vaccine each consisting of 2 ml. is shown in Fig. 1 for the three virus types; the responses to two doses are shown as black circles and those to three doses are shown as open circles.

In general the results were disappointing for all three types. In the case of those infants with no maternal antibody the responses to three doses (6 ml.) were very much better than those to two doses (4 ml.). After two doses, only 1 of 9 responded to type 1, 4 of 8 to type 2, and 6 of 9 to type 3, whereas after three doses the

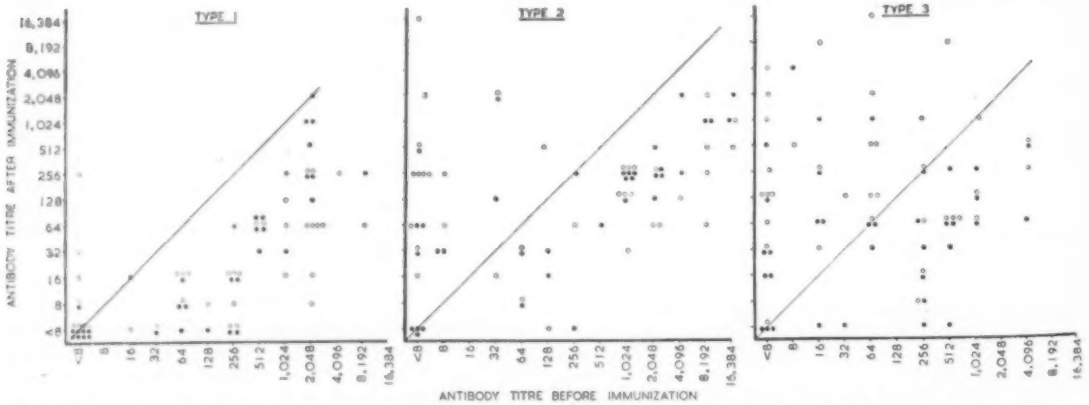


FIG. 1.—The response of 1-week-old infants to two and three doses of poliomyelitis vaccine. ●=Response after two doses ○=Response after three doses.

corresponding figures were 4 of 8, 10 of 10, and 9 of 10. The higher activity of the three-dose schedule was also evident from the increase in antibody levels, especially for types 2 and 3, the mean titres after two doses being 1, 6, and 14 and after three doses 6, 274, and 157 for types 1, 2, and 3 respectively.

In the case of those infants with maternal antibody, it is seen from the figures that with each type a high proportion showed no apparent responses. It is also seen that there were no striking differences between the responses to two and three doses. With type 1, no responses were observed after either two or three doses; with type 2 there were four after two doses and four also after three doses; with type 3, six responded after two doses and 13 after three.

It is interesting to note that for those infants with high maternal antibody levels to types 1 and 2—namely, those with a titre of 2,048 or more—the responses after three doses were in almost all cases lower than those after two. This was no doubt due to the fall off in maternal antibody levels during the period between the second and third doses. For those infants with intermediate maternal antibody levels—titres from 16 to 1,024—the third dose appeared to have had little effect with types 1 and 2, but with type 3 many of the infants gave an increase in antibody levels.

Response of 16-weeks-old Infants to Two and Three Doses of Vaccine

The antibody responses of the 16-weeks-old infants are shown in Figs. 2 and 3. It is seen that those infants with no maternal antibody (Fig. 2) responded better to three doses of vaccine than to two. This was shown both by the proportion of infants responding and by the values of the geometric mean titres. For type 1, 7 of 22 responded to two doses, with a mean titre of 3, and 20 of 24 to three doses, with a mean titre of 23. For type 2, all the infants responded to both two and three doses, but the mean titre of 83 obtained after two was substantially less than that of 477 after three doses.

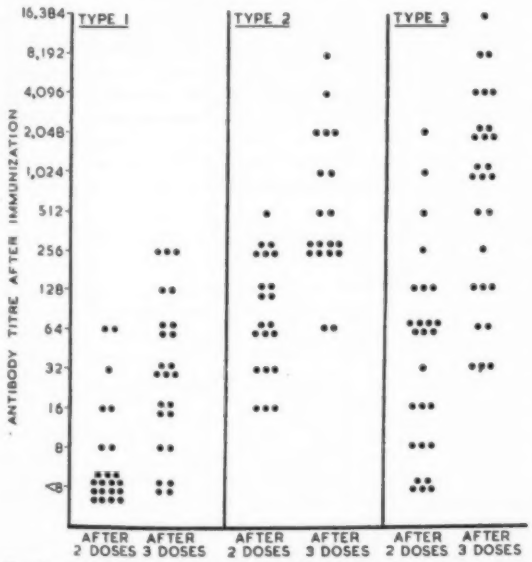


FIG. 2.—The response of 16-weeks-old infants with no maternal antibody to two and three doses of poliomyelitis vaccine.

For type 3, 21 of 26 responded to two doses with a mean titre of 30 and all responded to three doses with a mean titre of 695.

The results obtained in those infants with maternal antibody before immunization also showed that three doses of vaccine gave better responses than two. For type 1, only 3 of 27 infants had increased antibody levels after two doses compared with 9 of 25 after three doses; for type 2, 11 of 28 responded to two doses compared with 18 of 29 to three doses; and for type 3, 12 of 23 infants responded to two doses and 20 of 22 to three.

It is to be noted that the responses to types 1 and 2 with three doses of vaccine show evidence of maternal antibody interference. With type 1, 6 of the 11 infants with maternal antibody levels of 32 or less had titres greater than any of the 14 infants in whom the maternal antibody level was 64 or more. With type 2, 12 of 13 infants with maternal antibody levels of 32 or less responded, compared with 6 of 16 infants with maternal antibody levels of 64 or more. With type 3, however, there was less evidence of maternal antibody interference, but this was undoubtedly due to the lower levels of maternal antibody to this type and possibly to the greater antigenicity of this component of the vaccine.

Discussion

The incidence of maternally transmitted antibodies in the infants in this study was very similar to that of the infants previously recorded, and the loss of maternal antibody during the first 16 weeks of life was consistent with the previous findings that the level was halved approximately every 21 days.

It is evident from the results with the 1-week-old infants that the responses to two doses, each of 2 ml., were no better than those obtained previously in a similar group given two doses, each of 1 ml. On the other hand, three doses, each of 2 ml., produced a better response, but even with this schedule there was a high proportion of non-responders to all three types, particularly to type 1 and also among those infants possessing maternal antibody. In general, the responses to the three-dose schedule were no better than those obtained in the previous investigation in which 6-weeks-old infants were given two doses, each of 1 ml. It is thus difficult to know whether the increased responses to three doses were a result of the greater antigenic stimulus or of the increased age of the infants and hence their lower maternal antibody levels at the time of the third dose. It is probable that both factors play a part, but nevertheless it is quite clear that immunization at the age of 1 week, either with a two- or three-dose schedule or with a larger volume of vaccine, does not produce satisfactory results.

With the 16-weeks-old infants more encouraging results were obtained. With those who had little or no maternal antibody the responses to two doses, each of 1 ml., were no better than had been obtained in the previous study with 10-weeks-old infants on a similar schedule. On the other hand, three doses gave a decided improvement, 83% of the infants responding to type 1 and all to types 2 and 3; the geometric mean antibody titres reflected the greater immunizing power of the three-dose schedule.

Although a high proportion of infants with no maternal antibody responded to immunization, less

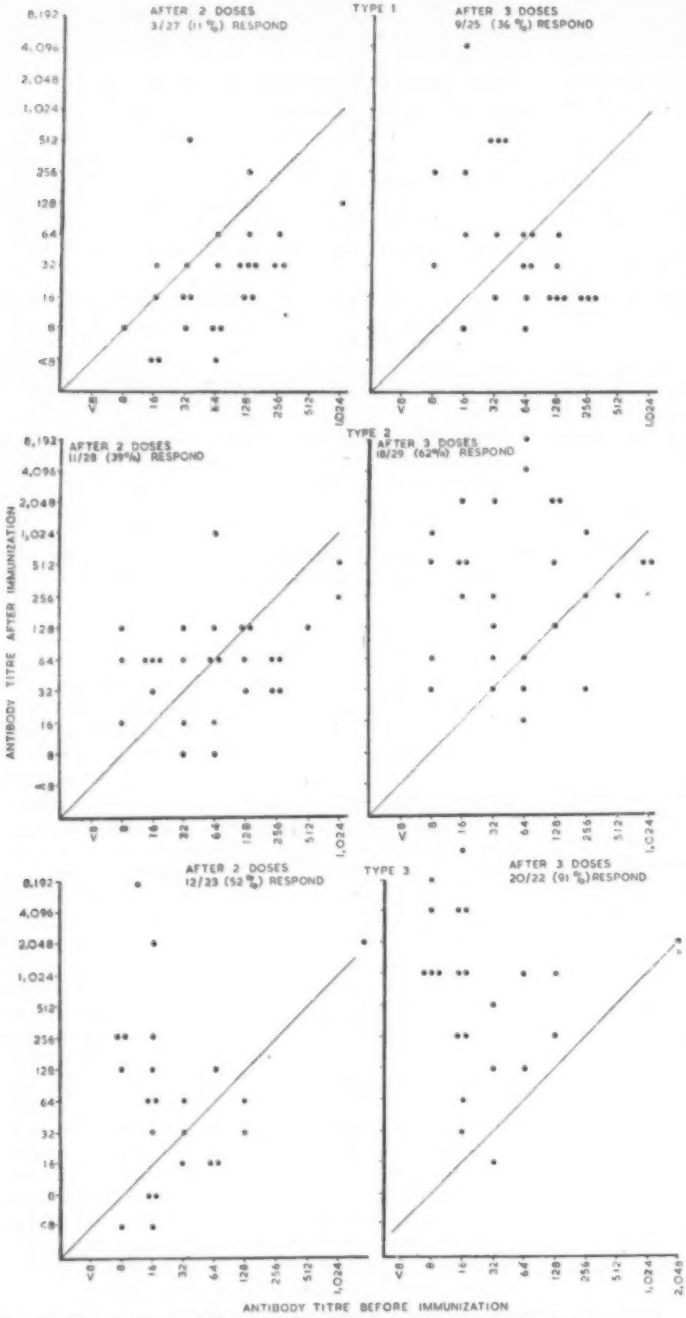


FIG. 3.—The response of 16-weeks-old infants with maternal antibody to two and three doses of poliomyelitis vaccine.

satisfactory results were obtained with those who had maternal antibody. After two doses, only 11% responded to type 1, 39% to type 2, and 52% to type 3, and after three doses the corresponding figures were 36%, 62%, and 91%. It is thus evident that the three-dose schedule was unable in all cases to overcome the maternal antibody interference, especially with type 1. It is probable, however, that these figures do not give an entirely true picture of the actual number responding to primary immunization, since in some cases the response may not be apparent because of masking by maternal antibody; the true picture will be revealed when a booster dose is given in a year's time. Nevertheless, the present results provide ample evidence to indicate that maternal antibody interference is occurring.

It is clear that, of all the groups so far studied, the 16-weeks-old infant, when given three doses of vaccine, responded best. This response, however, cannot be considered satisfactory, because immunization has not been achieved in all infants, especially in the case of type 1—the most important component of the vaccine. It would therefore seem advisable—as we have said previously—to delay immunization against poliomyelitis until maternal antibody has reached a non-inhibitory level.

Summary

The response of infants to poliomyelitis vaccine is governed by two factors—the level of maternal antibody and the number of antigenic stimuli given in the course of primary immunization. Two groups of infants, 45 aged 1 week and 55 aged 16 weeks, were studied. The 1-week-old infants had such high levels of maternal antibody that doubling the volume and giving three doses of vaccine resulted in no better response than that given by the normal immunization schedule in similar infants in the previous study. Satisfactory responses were obtained with the ordinary dose of 1 ml. in the 16-weeks-old infants who had very low maternal antibody levels, especially after the third dose of vaccine. In this age group, however, inhibitory levels of maternal antibody were present in some infants, and in order to obtain satisfactory immunization to all types in all infants it is suggested that immunization should be delayed until 6 to 9 months of age, at which time three doses of vaccine should be considered as a course of primary immunization.

Our thanks are due to Dr. G. V. Feldman, Dr. R. F. Jennison, and the nursing and laboratory staff at St. Mary's Maternity Hospital, Manchester, for their assistance, and to Miss K. South and Miss P. Tumber, of the Biological Standards Control Laboratory, London, for their help in titrating the sera. We also thank the Ministry of Health for the supply of poliomyelitis vaccine. This work was supported in part by a grant from the National Fund for Poliomyelitis Research to the Department of Child Health, Manchester University, for which we are most grateful.

REFERENCES

Perkins, F. T., Yetts, R., and Gaisford, W. (1958). *Brit. med. J.*, **2**, 68.

—— —— —— (1959). Ibid., **1**, 680.

PHENYLBUTAZONE AND ITS DERIVATIVES

WITH SPECIAL REFERENCE TO G.27202

BY

F. DUDLEY HART, M.D., F.R.C.P.
Assistant Physician and Physician-in-Charge, Rheumatism Unit, Westminster Hospital

AND

DENIS BURLEY, M.B., B.S.
Lately Medical Registrar, Westminster Hospital

In 1951 Currie reported on the use of phenylbutazone in the treatment of 41 cases of "fibrositis." As a result of this work one of us (F. D. H.) became interested in this compound and began blind controlled trials with material sent to him by Currie. The following year Currie (1952) published results on his first 81 patients, Hart and Johnson (1952) on their first 16, and the new substance was generally released. Since then it has been in extensive general use, and its efficacy and also its toxic effects have become widely recognized. Many consider it to be probably the best drug available, if tolerated, in the treatment of acute gout and all stages of ankylosing spondylitis (Hart, 1958), and in some cases of rheumatoid arthritis (Mason and Hayter, 1958). We agree with the last-named authors that it is often useful in other disorders of bone, such as metastatic carcinomatosis and Paget's disease. We also use it widely in the treatment of osteoarthritis, particularly of the hips. Such a wide spectrum of therapeutic efficiency has from the beginning made us feel that the good effect of the drug lies essentially in its giving relief from pain, and we have from early days regarded it from the clinical aspect as essentially a long-acting slowly broken down analgesic, its main virtue lying in its even action over 24 hours of the day. Graham (1958) also found it useful in three out of five cases of post-herpetic neuralgia, as did Partelides (1955) in a larger series, and we have obtained pain relief in a case of disseminated sclerosis where no bone or joint disease was present.

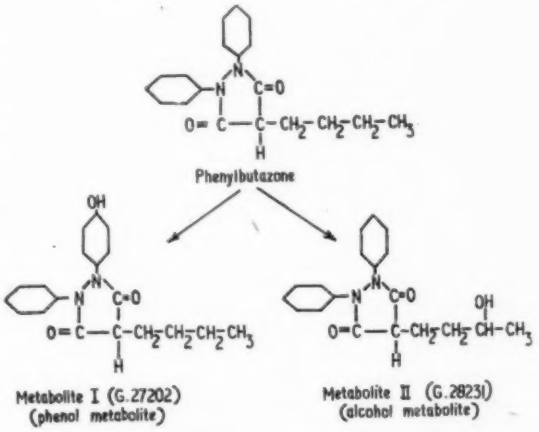
The relatively high incidence of gastro-intestinal side-effects has, however, led to increased efforts to find a derivative which would be better tolerated without significant reduction in therapeutic activity. The present paper concerns such a substance, now known as G. 27202 or "metabolite I."

Chemistry and Pharmacology

Burns *et al.* (1955b) investigated the metabolism of phenylbutazone and isolated two metabolites from the urine of patients receiving the drug. These two metabolites, metabolite I with a phenolic group in the para-position of a benzene ring, and metabolite II with an alcohol group in the butyl side-chain, are related as shown in the next column.

These two derivatives are identical with two pyrazole compounds which have been synthesized in Basle (Pfister and Häfliger, 1957; Denss *et al.*, 1957), and metabolite I, hydroxyphenyl butazone, has been designated G.27202. Biochemical analysis shows that when phenylbutazone is metabolized 3% appears in the urine as G.27202. If this substance is injected intravenously, like phenylbutazone, it disappears only slowly from the plasma, having an average biological half-life of three days (Burns *et al.*, 1953; Burns *et al.*, 1955a; Yü *et al.*, 1958). As only 4% of a given dose is excreted in the urine during this period of time it can be deduced that G.27202 is slowly but largely metabolized.

Oral absorption of G.27202 has been compared with intravenous administration in doses of 600 mg. (Yü *et al.*, 1958). Over a period of 4 to 24 hours these writers found that plasma levels were approximately the same by either route of administration, indicating extremely satisfactory absorption from the gastro-intestinal tract. With repeated orally administrated daily doses a plateau is reached in plasma level after three days; thereafter the level is constant from day to day for a given individual. The plasma levels had a range similar to that obtained with the same dosage schedule of phenylbutazone (Burns *et al.*, 1953).



The effect of G.27202 on the urinary excretion of sodium and water was also studied, as was its influence on the urinary excretion of uric acid (Yü *et al.*, 1958). It was found that, with doses of 800 mg. daily, sodium and water was retained in the body to a significant degree and similar to an equivalent dose of phenylbutazone. In contrast with phenylbutazone, however, there was no detectable uricosuria in doses of up to 800 mg. of G.27202.

Researches with metabolite II indicate that it is unlikely to be of clinical value as it is not absorbed orally, but it is interesting to note that administered intravenously, as one might have predicted, it is a potent uricosuric agent comparable to phenylbutazone and with a much reduced salt-and-water-holding power. The same workers found that various substitutions in the para-position of a benzene ring of phenylbutazone lead to compounds possessing potent "antirheumatic" and sodium-retaining activity. On the other hand, substitutions in the butyl side-chain result in compounds which have potent uricosuric activity but only mild "antirheumatic" and sodium-retaining properties.

Preliminary animal work with G.27202 has suggested that it is rather better than phenylbutazone as an anti-inflammatory and analgesic agent, the former being stressed as a result of its ability to reduce acute formalin oedema and formalin peritonitis in the rat (Domenjoz and Wilhelmi, personal communication). Also in that animal it partially inhibits the formation of inflammatory granuloma tissue (Selye's method). Of great significance to us was the finding of definite reduction in ulcerogenic activity from toxicity studies

in both dogs and rats with G.27202 as compared with the parent substance.

The promising results obtained from experimental work in both animals and humans prompted us to carry out a clinical trial with G.27202 in both in-patients and out-patients attending the rheumatism unit at Westminster Hospital.

Material and Methods

We treated 117 patients (52 male, 65 female) having the following disorders:

	Male	Female
Rheumatoid arthritis	21	41
Ankylosing spondylitis	22	3
Osteoarthritis	7	19
Psoriatic arthropathy	1	—
Paget's disease of femur	—	1
Sciatica (lumbar disk lesion)	—	1
Reiter's syndrome	1	—

Initially we set out to determine: (*a*) Whether patients obtained more or less relief of discomfort (pain and stiffness) on G.27202 as compared with phenylbutazone in the same dosage. (*b*) Which drug caused fewer symptoms of gastric intolerance. The method used was simply to substitute G.27202 for ordinary phenylbutazone dose for dose (usually 100 mg. b.d., t.d.s., or q.d.s.), the tablets being administered with meals. In all cases patients were put on each drug for one to three weeks unless gastro-intestinal symptoms necessitated discontinuing them. At the end of the trial they were asked to comment on which drug was the more effective (G>P or P>G), if both were equally effective (G=P), or if neither was effective (G=P=O). Comments on the side-effects and observations on fluid retention were also recorded.

In some of those patients who had found G.27202 effective, but less so than phenylbutazone, the dosage of G.27202 was subsequently increased to determine how much was required to obtain an equivalent effect. There were 14 patients in this group, and most of them were suffering from ankylosing spondylitis, as it was soon apparent that they were the best and most consistent observers.

In 10 cases the dose of G.27202 was increased up to 600 mg. to see whether symptoms of gastric intolerance appeared at this higher level. In 14 others the drug was continued for periods of 3 to 12 months to assess chronic toxicity.

Results

The observations on the relative effectiveness of G.27202 and phenylbutazone in the 117 patients are recorded in Table I by sex and collectively. It will be

TABLE I.—*Patients' Subjective Impressions of the Relative Effectiveness of Phenylbutazone and G.27202*

Sex	G>P	G=P	P>G	G=P=O	Total
Males	10 (19%)	17 (32%)	18 (35%)	7 (14%)	52 (100%)
Females	8 (13%)	17 (26%)	19 (29%)	21 (32%)	65 (100%)
Total	18 (15%)	34 (29%)	37 (32%)	28 (24%)	117 (100%)

Percentages are expressed separately for males, females, and the total.

seen that over twice as many females as males (32% to 14%) were not helped by either phenylbutazone or G.27202, but, excluding these, there is good agreement between the sexes as to the relative benefit obtained from the two preparations. Of the 89 patients helped by both phenylbutazone and G.27202, 34 considered the drugs to be of equal value, but of the remaining 55 twice as many thought phenylbutazone to be the stronger as thought the reverse (37 to 18).

As some patients were assessed and treated in hospital it was thought useful to see whether there were any different trends in response. The results are shown in Table II. There is little difference except that a larger

TABLE II.—*In-patients' and Out-patients' Subjective Impressions of the Relative Effectiveness of Phenylbutazone and G.27202*

	G>P	G=P	P>G	G=P=O	Total
In-patients	8 (18%)	11 (25%)	11 (25%)	14 (32%)	44 (100%)
Out-patients	10 (14%)	23 (31%)	26 (36%)	14 (19%)	73 (100%)
Total	18 (15%)	34 (29%)	37 (32%)	28 (24%)	117 (100%)

Percentages are expressed separately for in-patients, out-patients, and the total.

proportion of hospital in-patients did not benefit from either phenylbutazone or G.27202, possibly because their symptoms were more severe.

Of the 14 patients previously referred to who considered G.27202 less effective than phenylbutazone the effective dose ratio was found to be 2 to 1 in five patients, 5 to 3 in one, and 3 to 2 in eight, all in favour of phenylbutazone.

Long-term Study.—In the 14 patients treated with G.27202 for periods of 3 to 12 months there was no evidence of intolerance in any with a daily dose of 300–400 mg.

High-dosage Study.—In the 10 patients who had had gastric symptoms with phenylbutazone but who could tolerate G.27202, the dose of the latter was increased to 600 mg. daily for periods of one to three weeks. In one case mild indigestion appeared early but the remaining nine were unaffected.

Toxic and Side Effects

The number of patients who suffered from gastric intolerance with phenylbutazone was compared with those who had reacted in this way with G.27202. They were divided into those who had had mild indigestion which did not necessitate discontinuing treatment and those who had had treatment discontinued because of severe symptoms. The results are shown in Table III.

TABLE III.—*Gastric Intolerance in 117 Patients on Phenylbutazone and G.27202*

Gastric Intolerance	G.27202	Phenylbutazone
Severe symptoms	4	20
Mild ,,	6	5
Total	10	25

It will be seen that 25 out of the 117 patients had gastric intolerance to phenylbutazone whereas only 10 were similarly affected by G.27202. Furthermore, most of the cases intolerant to phenylbutazone had severe symptoms, whereas over half of those intolerant to G.27202 had mild symptoms.

Although electrolyte studies were not made, evidence of fluid retention, as measured by weight gain and ankle oedema, was noted. On phenylbutazone two patients gained weight and developed ankle oedema, and in one other there was slight weight gain. On G.27202 three patients gained weight and developed ankle oedema, and in two others there was slight weight gain. Other side-effects noted were an urticarial rash with fever which developed on the third day of G.27202 therapy and took a week to clear. Two others complained of giddiness and headache on both

phenylbutazone and G.27202; the significance of these complaints is difficult to assess. In no case was there any evidence of depression of circulating neutrophils.

Discussion

We have used phenylbutazone widely since 1952 in doses of 300–400 mg. daily, and to date we have met no case of agranulocytosis at this conservative dosage. Humble (1953) did, however, report that of 44 of our patients treated with phenylbutazone the blood clotting-time was significantly prolonged in 6 and in 14 the prothrombin time was prolonged.

Undoubtedly we would have used phenylbutazone even more widely had it not been for the occurrence of gastric intolerance in 20–25% of cases in which the therapy was instituted. In G.27202 we have a related substance which, on our experience, has a decidedly reduced liability to cause gastro-intestinal disturbance. Doses up to 600 mg. are in most cases well tolerated. This advantage is offset to some extent because, dose for dose, G.27202 appears to be a somewhat weaker pain-relieving drug than phenylbutazone.

It is true that some patients found G.27202 more effective than phenylbutazone, but many of these were intolerant of the latter, and this was sufficient to outweigh any consideration of reduced therapeutic effectiveness. We formed the opinion from a limited study, largely in cases of ankylosing spondylitis which benefited from both drugs, that phenylbutazone was more effective than G.27202 in the proportion of 3 to 2, with some patient-to-patient variation either side of this mean.

From experimental work in doses of 800 mg. daily G.27202 was shown to have a significant sodium-and-water-retaining activity comparable to that of the same dose of phenylbutazone (Yü *et al.*, 1958). In our study, using doses of 300–400 mg. daily, fluid retention was detected clinically in a small number of cases rather more with G.27202 than with phenylbutazone.

As a result of this investigation we have created a demand for G.27202 in a proportion of patients who obtain great benefit from it but who cannot tolerate phenylbutazone. This in itself is a persuasive argument for the introduction of an effective more benign phenylbutazone derivative. G.27202 goes some way to meet this demand and indicates that further adaptation of the original molecule may eventually produce the ideal "pain-relieving" preparation in the treatment of rheumatic diseases. The expression "pain relieving" is used advisedly because we have not personally observed any significant anti-inflammatory effect on swollen joints with this class of compound, and the term antirheumatic is too vague for clear interpretation.

It has already been mentioned that substitutions in the benzene ring increase the salt-retaining and pain-relieving properties of the parent substance, whereas substitutions in the butyl side-chain enhance uricosuric activity. It also appears that those substitutions which cause a reduction in the *p*K value are the ones which produce the greatest uricosuric activity, and recently the phenylthioethyl derivative of metabolite II, designated G.25671, and the sulphoxy metabolite G.28315 have been investigated (Ogryzlo and Harrison, 1957; Kersley *et al.*, 1958); both these derivatives are effective on oral administration and cause little or no gastric irritation. The above-mentioned workers have found that both these substances (G.25671 and G.28315) have a short half-life in the body and little pain-relieving activity or tendency to produce salt and water retention; for this reason they were recommended in the treatment of chronic gout, in which condition they compared favourably with other uricosuric agents. It appears to us that G.27202 is likely to be of value in the treatment of acute gout, where the possibility of giving doses up to 800 mg. daily without significant gastric toxicity will be of great advantage.

Work has to date been centred more on the uricosuric compounds than on the "antirheumatic" ones. From our series of cases we feel that further modifications may produce less toxic and more useful compounds in the treatment of a large variety of the chronic rheumatic disorders.

Summary

G.27202 (hydroxy-phenylbutazone), a metabolite of phenylbutazone, given in equal doses, has been shown to cause considerably less gastric irritation in our hands than phenylbutazone itself. Although long-term continued studies may reveal a larger number of side-effects, these have to date been infrequent and mild with a daily dose of 100–600 mg. taken orally with meals.

The pain-relieving properties of G.27202 vary from patient to patient, but overall it appears to be weaker than phenylbutazone, possibly in the ratio of 3 to 2. This reduction in effectiveness, however, only slightly offsets the more definite reduction in gastric irritation.

There are distinct advantages in using a slowly metabolized long-acting substance in the treatment of the chronic rheumatic disorders; G.27202 may well play a useful part in those cases where phenylbutazone is poorly tolerated.

Our thanks are due to Dr. W. S. Stoddart, of Geigy Pharmaceuticals Ltd., for his assistance in the preparation of this paper and for the generous supplies of G.27202.

References

Burns, J. J., *et al.* (1953). *J. Pharmacol. exp. Ther.*, **109**, 346.
—— (1955a). *Fed. Proc.*, **14**, 323.
—— (1955b). *J. Pharmacol. exp. Ther.*, **113**, 9.
Currie, J. P. (1951). *II Congreso Europeo de Reumatologia; Barcelona: Comunicaciones*, p. 417.
—— (1952). *Lancet*, **2**, 15.
Denss, R., Häfliger, F., and Goodwin, S. (1957). *Helv. chim. Acta*, **40**, 402.
Graham, W. (1958). *Canad. med. Ass. J.*, **79**, 634.
Hart, F. D. (1958). *Brit. med. J.*, **2**, 1082.
—— and Johnson, A. M. (1952). *Lancet*, **2**, 43, 197, 587.
Humble, J. G. (1953). *Brit. med. J.*, **2**, 1214.
Kersley, G. D., Cook, E. R., and Tovey, D. C. J. (1958). *Ann. rheum. Dis.*, **17**, 326.
Mason, R. M., and Hayter, R. R. P. (1958). *Practitioner*, **181**, 23.
Ogryzlo, M. A., and Harrison, Joan (1957). *Ann. rheum. Dis.*, **16**, 425.
Partelides, G. (1955). *Lancet*, **2**, 1142.
Pfister, R., and Häfliger, F. (1957). *Helv. chim. Acta*, **40**, 395.
Yü, T. F., *et al.* (1958). *J. Pharmacol. exp. Ther.*, **123**, 63.

Statistics on the medical profession in Africa compiled by the W.H.O. show that in Algeria there is one doctor for every 4,958 of the population, one per 5,708 in Tunisia, 9,926 in Madagascar, 9,263 in Morocco, 9,924 in Kenya, 20,166 in the Cameroons under French trusteeship, 20,203 in Tanganyika, 20,379 in the Belgian Congo, 21,022 in Uganda, 23,028 in French Equatorial Africa, 29,197 in French West Africa, 29,761 in Liberia, 55,057 in Nigeria, 62,630 in the Cameroons under British trusteeship, and 65,146 in Ruanda-Urundi. By way of comparison with other continents, the United States has 729 inhabitants to each doctor, France 1,090, the United Kingdom 1,855, Brazil 2,993, and Indonesia 71,465 (*Science-Afrique*, No. 13, 1958).

SMOKING HABITS OF MONOZYGOTIC AND DIZYGOTIC TWINS

BY

LARS FRIBERG, M.D.

LENNART KAIJ, M.D.

SVEN J. DENCKER, M.D.

AND

ERLAND JONSSON, Ph.D.

From the Institute of Hygiene, Karolinska Institute, Stockholm, the Psychiatric Department, University of Lund, and the Department of Public Hygiene, the National Institute of Public Health, Stockholm

Various epidemiological investigations—for example, Doll and Hill (1954, 1956), and Hammond and Horn (1954)—have, independently of each other, demonstrated higher morbidity and mortality from, *inter alia*, cardiac disease and pulmonary cancer in tobacco smokers as compared with non-smokers. These findings have often been cited as evidence of a direct causal association between smoking and the diseases in question. The planning of the inquiries and the interpretation of results, however, have been sharply criticized from several quarters. For instance, it has been pointed out that in many respects smokers differ essentially from non-smokers, and for this reason comparison between the two groups is not entirely warrantable.

An important source of error in comparing smokers and non-smokers with respect to morbidity and mortality lies in the possibility of constitutional dissimilarities between the groups. It is thus conceivable that a common factor predisposes to the diseases as well as to excessive smoking. A study of a sufficient number of monozygotic twin pairs who differ in their smoking habits should substantially eliminate such sources of error and show the possibility of a causal connexion between smoking and disease.

Before an investigation of morbidity and mortality can be embarked upon, therefore, the smoking habits of twins must be charted. An inquiry of this type should also indicate the importance of the genotype in relation to smoking habits. If, for instance, it is found that twins of monozygotic pairs are more alike in smoking habits than twins of dizygotic pairs, the suggestion is that constitutional factors may significantly influence these habits.

Present Investigations

In all, 59 monozygotic and 59 dizygotic twin pairs were studied. These were taken from a series of 178 unselected twin pairs born at the obstetrical department of Lund University Hospital between 1900 and 1934 and described by Essen-Möller (1941). Essen-Möller divided this series into three groups. Group I comprised 43 pairs of monochorionic—true monozygotic—twins. Group III consisted of 73 pairs in which the blood groups differed according to the ABO and/or the MN system—definitely dizygotic twins. Group II contained the 62 remaining pairs: the twins of these pairs were apparently dichorionic, but were found to be alike with respect to the blood groupings employed, and thus constituted an uncertain group at the time of the original study.

By means of anthropological investigations by Essen-Möller (1941), supplemented by grouping of blood and serum—ABO, MNS, P, Duffy, Kell, Lewis, Rh, and Lutheran blood group systems, the Gm serum group according to Grubb, and haptoglobin groups according to Smithies—group II could be divided into 19 monozygotic and 43 dizygotic twin pairs. In only one pair was there a reasonable doubt of zygosity. The general impression was that this pair was dizygotic; it was therefore counted as such. (Further details of the blood groupings will be published by M. Hauge, L. Kaij, and S. J. Dencker.)

The 59 pairs of monozygotic twins comprised 40 pairs from Essen-Möller's group I and all of the 19 monozygotic pairs from group II. Our 59 dizygotic twin pairs comprised all but 4 of the remaining pairs from group II and 20 from group III, selected so as to match the monozygotic group for age and sex. The distribution of the case material according to age and sex is shown in Table I.

TABLE I.—*Age and Sex*

Zygosity	No. of Pairs		Year of Birth			
	Males	Females	1900–09	1910–19	1920–29	1930–34
Monozygotic ..	21	38	6	7	26	20
Dizygotic ..	21	38	3	8	29	19

Most of the twins were interviewed at personal visits from two of us (S. J. D. and L. K.). In a few cases the interview was conducted by telephone or, when this was not possible, by letter. A special questionary was used (important details of this are given in Appendix A).

The degree of concordance of smoking habits within the monozygotic and the dizygotic twin pairs was investigated by two methods.

1. The series was divided into four groups: regular smokers; sporadic smokers (less than one cigarette, cigarillo, or cigar a day); former smokers; and other non-smokers. Chi-square analysis (see, for example, Siegel, 1956) was then used to compare the respective frequencies of concordance of this grouping within monozygotic and dizygotic twin pairs.

2. Forty "adjudicators" (public health officers, medical students, and a few laboratory assistants) received the following information of the twin pairs (see example in Appendix B): sex; age; qualitative smoking habits (regular or sporadic smoker, etc.); type of tobacco used (cigarettes, pipe tobacco, etc.); amount of tobacco used; changes in this amount; and age at which the subject began and ceased smoking. From this information, but without knowing whether the various pairs were monozygotic or dizygotic twins, the adjudicators estimated the degree of concordance in smoking habits according to an 11-degree scale, in which 11 denoted maximal and 1 minimal resemblance. The twin pairs were then ranked in accordance with the scale values, and the placing of the monozygotic and the dizygotic pairs was compared. This comparison was made with the Mann–Whitney U test (see Siegel, 1956).

Results

Table II shows that the twins of monozygotic pairs belonged to the same group in 45 cases, whereas the corresponding figure among the dizygotic pairs was

TABLE II.—*Smoking Habits of the Twins (A=Regular Smokers, B=Sporadic Smokers, C=Former Smokers, D=Other Non-smokers)*

Monozygotic Pairs					Dizygotic Pairs				
Twin I	Twin II				Twin I	Twin II			
	A	B	C	D		A	B	C	D
A	*15*				A	*15*			
B	3	*3*			B	0	*0*		
C	3	0	*1*		C	7	0	*0*	
D	4	1	3	*26*	D	11	2	5	*19*

only 34. The chi-square analysis demonstrated a significantly greater proportion of concordant cases within the monozygotic group than within the dizygotic group ($0.01<P<0.05$).

Appendix C shows the rank number of each twin pair calculated from the median of the values given by the adjudicators. The sum for the monozygotic pairs was 3,076 and that for the dizygotic pairs 3,945 (in the rank-order the pairs with the highest median values—scale values—were given the lowest numbers).

The Mann–Whitney U test of the rank sums of both groups showed that the placing of the monozygotic pairs was significantly higher than that of the dizygotic pairs ($0.001<P<0.01$), which implies that concordance was greater within the monozygotic pairs. (The level of significance is not decreased even if pairs with rank numbers of 20.5 (see Appendix C) are excluded.)

Discussion

This investigation demonstrated greater concordance of smoking habits within monozygotic twin pairs than within dizygotic twin pairs. The difference was statistically significant concerning "qualitative" smoking habits as well as in estimations made from all data of smoking. Estimation of concordance may, of course, be made from other principles than those used in our study. It would seem, however, that the higher value in monozygotic twins will emerge in all appropriate methods. In our investigation we attributed special importance to the results based on appraisal by a large number of adjudicators who made their assessment on all the relevant data except zygosity.

How far may the results be said to indicate the importance of the genotype in relation to smoking habits? According to the conventional interpretation they imply that smoking habits are definitely influenced by constitutional factors. In recent years, however, this interpretation of investigations on twins has to some extent been challenged by writers such as Bleuler (1955), who pointed out that the environment of monozygotic twins may be more uniform than that of dizygotic twins. If this is true it must be particularly prominent as a source of error concerning factors which *a priori* can be classed as highly susceptible to environment, such as smoking habits. On the other hand, one may object that, as a rule, smoking habits are formed after the twins have passed the years of maximum unity.*

*After this article was written our attention was drawn to a paper by R. A. Fisher (*Nature (Lond.)*, 1958, **182**, 596) in which he reports the smoking habits of 27 monozygotic twin pairs brought up apart. The concordance rate in this group was as high in a comparable but non-separated monozygotic group. Although no detailed analysis is presented, this result contradicts the theory of mutual influence between the twins as a major cause of concordance and supports the view of genotropic influence on smoking habits.

To what extent our results may apply to other twin populations we have no certain knowledge. Quite independently of our inquiry, however, Fisher (1958) reported some preliminary observations in German twins. Although his material was not statistically analysed—possibly because the selection was not ideal—the tendencies in the results were identical with ours. It therefore seems probable that certain differences as regards smoking habits between monozygotic and dizygotic twin pairs are not confined to the fairly small population from which our material was collected.

Our investigation finally showed—and here, too, it received support from Fisher's findings—that in general a not insignificant proportion of monozygotic twin pairs may be expected to show discordance in regard to smoking habits. The feasibility of investigating the injurious effects of tobacco smoke from morbidity and mortality in twins will, of course, depend upon the number of twin pairs available. In this connexion, however, it should be pointed out that monozygotic twins who are concordant in smoking habits, and also dizygotic twins, constitute important groups for comparison. The number of discordant monozygotic twins, therefore, will not be the sole decisive factor.

Summary

A comparison between the smoking habits of 59 pairs of adult monozygotic twins and 59 pairs of adult dizygotic twins showed significantly greater concordance within the monozygotic pairs.

APPENDIX A. PART OF THE QUESTIONARY

Smoking Habits

10. Do you smoke ?: No. Yes. Indefinite reply.
11. *If "no" in point* 10. Did you smoke formerly ? No. Yes. Indefinite reply.
17. *If yes or indefinite in point* 10. What do you smoke ? Cigarettes. Cigars or cigarillos. Pipe.
18. *If yes or indefinite in point* 10. Do you smoke daily or sporadically ? Daily. Sporadically. Don't know.
19. *If yes or indefinite in point* 10. How much do you smoke ? Number of cigarettes per day. Number of cigars or cigarillos per day. A packet of tobacco (50 g.) lasts ..... days.
20. *If yes or indefinite in point* 10. How old were you when you began to smoke regularly ? .....years.
22. *If yes or indefinite in point* 10. Are you smoking more than you did five years ago ? More. Less. The same. Don't know.

APPENDIX B. EXAMPLES OF THE DATA FROM WHICH CONCORDANCE WAS ESTIMATED

Code No.
Sex: Males.
Born: 1927.
Twin A does not smoke now and has not smoked formerly.
Twin B does not smoke now and has not smoked formerly.

Code No.
Sex: Males.
Born: 1926.
Twin A does not smoke now, but formerly smoked 10 cigarettes per day. He began to smoke when he was 14 years old and ceased when he was 32.
Twin B smokes 15 cigarettes per day and sporadically smokes a pipe. He began to smoke when he was 15 years old and smokes less now than five years ago.

APPENDIX C. RANK NUMBERS OF THE TWIN PAIRS*

Monozygotic Pairs		Dizygotic Pairs	
118	47	117	71
108	46	115·5	67·5
105	45	115·5	66
104	43	114	63
103	42	113	61
99	41	112	58
97	20·5	111	55
92	20·5	110	54
90	20·5	109	51
88·5	20·5	107	50
84	20·5	106	49
81	20·5	102	44
79	20·5	101	20·5
79	20·5	100	20·5
79	20·5	98	20·5
76	20·5	96	20·5
74·5	20·5	95	20·5
71	20·5	93·5	20·5
69	20·5	93·5	20·5
67·5	20·5	91	20·5
65	20·5	88·5	20·5
64	20·5	87	20·5
62	20·5	86	20·5
60	20·5	85	20·5
59	20·5	83	20·5
57	20·5	82	20·5
56	20·5	77	20·5
53	20·5	74·5	20·5
52	20·5	73	20·5
48		71	
	3,076·0		3,945·0

* Rank-order based on the results of appraisal of all data. Low number signifies strong concordance.

REFERENCES

Bleuler, M. (1955). *Familial and Personal Background of Chronic Alcoholics: Etiology of Chronic Alcoholism*, edited by O. Diethelm, p. 110. Thomas, Springfield.
Doll, R., and Hill, A. B. (1954). *Brit. med. J.*, **1**, 1451.
—— —— (1956). Ibid., **2**, 1071.
Essen-Möller, E. (1941). *Hereditas (Lund)*, **27**, 1.
Fisher, R. A. (1958). *Nature (Lond.)*, **182**, 108.
Hammond, E. C., and Horn, D. (1954). *J. Amer. med. Ass.*, **155**, 1316.
Siegel, S. (1956) *Nonparametric Statistics for the Behavioral Sciences*. McGraw-Hill, New York.

Medical Memoranda

A Case of Anaemic Gangrene of the Bowel

Mesenteric vascular occlusion was first reported by Tiedman in 1843. From that time it was observed increasingly by Virchow, Moor, Hegar, and Chiene, until at the turn of the century Jackson, Porter, and Quinby, in America, were able to collect 214 cases. Leslie Trotter (1913) published an excellent and comprehensive monograph on the subject. He drew attention to a group of cases in which the intestines presented as a pale or "anaemic infarct" as distinct from the more commonly observed congested plum-coloured infarct. He quotes a series of nine cases. Eight were collected from the literature, the other was a case under the care of Sir Rickman Godlee reported by Trotter, who described the affected bowel as "white or yellowish grey in colour and entirely devoid of blood. At one or both ends of the infarcted segment there may be a demarcation zone of hyperaemia separating it from healthy intestine, as in the case of anaemic infarcts in other parts of the body. The wall of the affected coil is generally very thin."

CASE REPORT

A woman aged 76 was admitted to the Royal Hospital, Wolverhampton, on September 20, 1957, as a case of auricular fibrillation with severe abdominal pain of 22 hours' duration. Her general condition on admission was poor; she was collapsed, with a barely perceptible pulse and a blood pressure of 60/40. Her story, for she was quite lucid and mentally alert, was that one hour after her midday meal the previous day she was seized by severe central abdominal pain associated with some bilious vomiting. The pain gradually increased in severity, and after a restless night her general condition suddenly deteriorated, culminating in the collapsed state with which she presented in the casualty department.

Examination of the abdomen revealed a moderate degree of distension, with tenderness on the right spreading across the epigastrium. There was some guarding but no rigidity. Bowel sounds were absent. There had been absolute constipation since the onset of pain. Rectal examination did not reveal any blood or abnormally coloured faeces.

A straight *x*-ray film did not reveal any fluid levels but showed a peculiar gas shadow below the liver on the extreme right. Serum amylase was within the limits of normal.

The patient responded to sedation and the administration of intravenous fluids. Her blood pressure rose to 120/80 during the afternoon and stabilized at this level. At this point it was decided to perform a laparotomy.

Under general anaesthesia a laparotomy was performed through a paramedian incision. When the peritoneum was incised the odour of putrefaction arose. The intestines were bathed in a foul-smelling turbid fluid—not blood stained—and presented as a grey infarct with the proximal coil of jejunum plum-coloured, as were the terminal ileum and colon.

As the patient's general condition began to deteriorate rapidly an emergency closure was done and she was returned to the ward. She died that evening.

At the post-mortem examination, carried out by Dr. A. G. Marshall, an embolus was found to have lodged in the superior mesenteric artery just below the inferior pancreaticoduodenal branch. Progression clot was present in all the branches of the artery below this point. The heart was hypertrophied and the left auricular appendage was full of old thrombus: one piece was lying loose in the auricle.

COMMENT

The cause of this type of gangrene is obscure, in that it is difficult to account for the absence of reflux of portal blood. Moore (1941) recognized this rare condition in a survey of mesenteric vascular occlusion but was unable to explain its occurrence. Klass (1951) and Van Weel (1953) reported cases in which embolectomy was performed and which would fit into this category of anaemic gangrene. These gave a history of 12 and 13 hours' duration.

The case reported here was of at least 27 hours' duration when brought to laparotomy, and at least 18 hours had elapsed before circulatory collapse occurred.

No reasonable cause was found on post-mortem examination to account for the lack of reflux of portal blood when relieved of its normal *vis a tergo* by the impact of the embolus in the superior mesenteric artery. The portal vein and its tributaries were normal. The proximal jejunum and the caecum did, of course, show congestion of the more usual venous type.

I thank Mr. C. Vincent Patrick for his advice and permission to publish this case. Dr. A. G. Marshall kindly supplied the details of the post-mortem examination.

J. MCKESSAR DUNCAN, F.R.C.S.,
Late Senior Registrar, Queen Elizabeth Hospital, Birmingham.

BIBLIOGRAPHY

Cokkinis, A. J. (1926). *Mesenteric Vascular Occlusion*. Baillière, Tindall and Cox, London.
Ficarra, B. J. (1944). *Amer. J. Surg.*, **66**, 168.
Klass, A. A. (1951). *Ann. Surg.*, **134**, 913.
Moore, T. (1941). *Brit. J. Surg.*, **28**, 347.
Trotter, L. B. C. (1913). *Embolism and Thrombosis of Mesenteric Vessels*. University Press, Cambridge.
Van Weel, M. W. (1958). *Arch. chir. neerl.*, **6**, 149.

Reviews

BLOOD-GROUP GENETICS

Heredity of the Blood Groups. By Alexander S. Wiener, A.B., M.D., F.A.C.P., F.C.A.P., and Irving B. Wexler, A.B., M.D., F.A.C.P. (Pp. 150+x; illustrated. $6.) New York and London: Grune and Stratton. 1958.

This book is to be welcomed as giving in a more complete and systematic form than in any of his previous publications the views of the senior author on the genetics of the blood-group systems and especially of the Rh system. Apart from a general introduction, and final chapters on the medico-legal and anthropological applications of blood grouping, the book is devoted to a systematic survey of the genetics of each of the known blood-group systems. It is in most respects complete and up to date, bringing in, for example, recent complications and extensions of the P and Kell systems. The treatment of the Lewis system is, however, quite outdated. Scarcely anyone but the authors would now support a theory of three genes at a single locus. Not only Ceppellini, but also Grubb and Andresen have, on the basis of extensive series of tests, put forward theories requiring the interaction of genes at two non-linked loci, and differing from one another in detail rather than in principle, and it is clear that any of these theories accounts for the facts very much better than can any single locus theory.

Readers will, however, be apt to turn first to the chapter on the Rh–Hr system, to which 43 pages are devoted. Here they will find the well-known views of Wiener fully and conveniently set out, but with little that is new. They will also find the familiar criticisms of the views of Fisher and Race. Most of the chapter is written in terms of the "factors" which are commonly known to British readers as the genes C, D, E, c, and e, and it would be possible to transliterate the symbols in much of the first half of the chapter into the CDE notation with very little change of the sense. Because of the insistence on old and not generally accepted arguments certain important new facts adduced at the end of the chapter do not stand out as they should by contrast; for it is now becoming likely that certain recent discoveries in the Rh field will need for their explanation some extension of the simple theory of a chain of separate and separately acting though closely linked genes. Whatever may be the underlying genetical reality, the CDE notation is still for most purposes the more convenient, and in my opinion it is rather on the genetical than on the notational side that important arguments can be raised in favour of Wiener's views. It is therefore interesting to see that the authors themselves take quite the opposite view, for they say (p. 102): "The essential difference between the two concepts is on a serological, and not a genetic level. Blood grouping is a subspecialty of immunology, and while a knowledge of genetics is helpful, it is only of secondary importance for mastery of the field. The linkage theory completely evades the fundamental immunological concept of the difference between an agglutinogen and its serological attributes, the blood factors, and therein lie the pitfalls of the C-D-E notations. Thus, the issue at stake is not merely a choice between two nomenclatures, but the accuracy in reporting scientific observation."

A. E. MOURANT.

EYE IN HEALTH AND DISEASE

The Preservation of Eyesight. Prepared with the advice of a Consultative Committee, and edited by Sir Arthur Salusbury MacNalty, K.C.B., M.A., M.D.(Oxon.), F.R.C.P.(Lond.), F.R.C.S.(Eng.), D.P.H., Hon.F.R.S.(Edin.). (Pp. 107+vi; illustrated. 12s. 6d.) Bristol: John Wright and Sons Ltd. 1958.

Sir Arthur MacNalty's interest in the problems of preservation of eyesight is well known. His *Eyes in Industry* helped to draw attention to the considerable industrial problems of ophthalmology. In this small book he has aimed at a larger audience—lay as well as medical. The ophthalmic surgeons, general practitioners, and medical students to whom he addresses himself will find here a simple and clear statement on the structure, function, and disorders of the eye, whilst nurses, health visitors, health educators, and school-teachers—the rest of the audience he addresses—should find this particularly useful in giving an authoritative account in simple language of the problems of the eye in health and disease. He has had the assistance of a small committee in preparing this little book, and this has helped to produce a balanced and accurate presentation—something rather uncommon in popular books.

ARNOLD SORSBY.

INJURY AND FRACTURE

Fractures and Other Injuries. Edited by Edwin F. Cave, M.D. (Pp. 863+xvii; illustrated. £10 10s.) Chicago: The Year Book Publishers, Inc. London: Interscience Publishers, Ltd. 1958.

All dedications are suspect, but not all are grammatically suspect; this is "Dedicated to the 'Spirit of Teaching,' so loyally carried out over the years by the faculty of the Harvard Medical School and by members of the Massachusetts General Hospital Fracture Clinic — past, present, and future." Fortunately the impression made by the first words which catch one's eye on opening the book is not borne out by the rest of the volume, which is clearly and satisfactorily written. A standard of uniformly excellent illustrations has been achieved by the Massachusetts Hospital Art Department. Uniformity is not so apparent in the text, which is really a series of essays by staff associated with the hospital, so chosen and arranged that they cover every aspect of injury. The volume thus falls into line with the recent tendency to treat injury as a whole and not limit the discussion to fractures alone. It is primarily a student's textbook and not a specialist's volume. The influence of Lottes, at one time a member of the hospital staff, is shown in the chapter on fractures of the tibia, where it is stated that "any fracture in the middle third or upper portion of the lower third of the shaft of the tibia is suitable for nailing." Böhler's comments on this statement would be unprintable. The use of plates is rightly condemned in fractures of the femur and a Küntscher nail recommended. The convenient correction of minor angular deformities in fractures of both bones of the leg by wedging the plaster is not mentioned.

Although the chapter on fractures of the ankle shows familiarity with the best authors, it is the least satisfactory. Dealing with a subject which in enthusiastic hands tends to outgrow the space available, there should be no time for remarks such as "the best time to reduce any fracture is immediately after it

occurs." This has been emphasized in the introduction, and the space might well be given to a discussion on diastasis or to the varieties of fracture of the medial malleolus, which are lacking. The chapter limits itself to the general care of ankle fractures, and remains dull and uninteresting, if practical.

The volume is a sound guide to trauma and its treatment, of particular interest to the students of the Massachusetts General Hospital, who will be familiar with the minor peculiarities of the several authors. It contains clearly and succinctly the fundamental facts of the care of injury ; and without a grasp of these it is far better to pass by on the other side of the road than attend the accident, if one is certain that a traumatologist is following behind one ; and nowadays one probably is.

J. G. BONNIN.

SKULL FRACTURES

Injuries of the Bones of the Head. An Atlas of Clinical and X-ray Diagnosis. By J. Vondra, M.D., and R. Blaha, M.D. (Pp. 304; illustrated. 40s.) Prague: Artia. London: Constable and Co., Ltd. 1958.

This book claims to be an atlas of clinical and radiological diagnosis, and it includes all the bones of the skull ; one author is an oral and maxillo-facial surgeon and other a radiologist. If the book had been restricted to those fractures which come within the scope of maxillo-facial surgery it would have been smaller and helpful to those to whom it is directed—"busy doctors in health centres and out-patients' departments." As it is, the book is swollen with descriptions of fractures through various parts of the skull vault and base, academically of some interest but certainly of no significance for the "busy doctor." and with practically no observations on the diagnosis of brain damage. The atlas consists of 170 illustrations—the majority are of radiographs ; some are of the skull, depicting the commoner types of fracture of the maxilla and mandible—quite useful. It is unfortunate that so many of the radiographs fail to reveal the fracture described in the legend because reproduction is so bad.

D. W. C. NORTHFIELD.

PATHOLOGY OF THE MOUTH

A Textbook of Oral Pathology. By William G. Shafer, B.S., D.D.S., M.S., Maynard K. Hine, D.D.S., M.S., and Barnet M. Levy, A.B., D.D.S., M.S. (Pp. 714+viii; illustrated. £5 5s.) London and Philadelphia: W. B. Saunders Company. 1958.

This is a pleasant and well-illustrated book. It is somewhat unusually arranged in five sections, the first being "Disturbances of Development and Growth," the second "Diseases of Microbial Origin," the third "Injuries and Repair," the fourth "Disturbances of Metabolism," and the fifth "Diseases of Specific Systems," having relation to oral conditions. It also has a somewhat wider background than in most books of this type, and the short discussion on the normal physiology before reference to pathological conditions renders the book far more useful and intelligible to the student. Very adequate references are given for further reading, and in an appendix useful tables can be found for normal values of varying types of laboratory investigations. Altogether a good, sensible, and readable book.

A. B. MACGREGOR.

BOOKS RECEIVED

Review is not precluded by notice here of books recently received

Suicide in Hong Kong. With Special Reference to Attempted Suicide. By P. M. Yap, M.A., M.D.Cantab., M.R.C.P.Edin., D.P.M.Lond. Foreword by Martin Roth. (Pp. 101. 12s. 6d.) Hong Kong: University Press. London: Oxford University Press. 1958.

Official History of New Zealand in the Second World War, 1939-1945. Medical Services in New Zealand and the Pacific, in Royal New Zealand Navy, Royal New Zealand Air Force and with Prisoners of War. By T. Duncan Stout, M.B., M.S.(Lond.), F.R.C.S.(Eng.), F.R.A.C.S. (Pp. 450+xiv; illustrated.) Wellington, New Zealand: War History Branch, Department of Internal Affairs. 1958.

Konservative und Chirurgische Behandlung angeborener und erworbener Herzfehler. Drei Vorträge. By Professor E. Debra, M.D., Professor O. Bayer, M.D., and H. H. Wolter, M.D. (Pp. 64+vii: illustrated. DM. 6.40.) Stuttgart: Georg Thieme Verlag. 1959.

Die Laparoskopie und die Culdoskopie in der Gynäkologie. By Dr. H. Frangenheim. (Pp. 70+viii; illustrated. DM. 19.80.) Stuttgart: Georg Thieme Verlag. 1959.

Gastric Cancer in Saskatchewan, 1932-1955. By T. H. Crawford Barclay, Ch.M., F.R.F.P.S.G. (Pp. 208; illustrated. Gratis.) Regina: Saskatchewan Cancer Commission. Department of Public Health of Saskatchewan. 1958.

Results of Treatment of Cancer in Saskatchewan 1945-52 (inclusive). By T. A. Watson, M.B., Ch.B., D.M.R. (Pp. 76. Gratis.) Regina, Saskatchewan: Province of Saskatchewan, Department of Public Health. 1958.

Strabismes, Hétérophories, Paralysies Oculo-Motrices. (Les Déséquilibres Oculo-Moteurs en Clinique.) By René Hugonnier. (Pp. 748+viii; illustrated. 8,500 fr.) Paris: Masson et Cie. 1959.

L'Ophtalmologie Française au XXe Siècle. Les Progrès de L'Enseignement, de la Clinique et de la Thérapeutique. By René Onfray. (Pp. 236. 3,600 fr.) Paris: Masson et Cie. 1959.

Manuel de Traumatologie (Membres–Rachis–Ceintures). By Georges Rieunau. (Pp. 220; illustrated. 3,000 fr.) Paris: Masson et Cie. 1958

Comprehensive Medical Services under Voluntary Health Insurance. A Study of the Windsor Medical Services. By Benjamin J. Darsky, M.A., Nathan Sinai, Dr.P.H., and Solomon J. Axelrod, M.D., M.P.H. (Pp. 392+xvii. 60s.) Cambridge, Massachusetts: Harvard University Press. London: Oxford University Press. 1958.

The Recovery Room. A Symposium. By John Adriani, M.D., and John B. Parmley, M.D. (Pp. 123+xii; illustrated. 32s. 6d.) Oxford: Blackwell Scientific Publications. 1958.

Clinical Orthopaedics. No. 12. Edited by Anthony F. DePalma. (Pp. 327+xii; illustrated. 60s.) Philadelphia and Montreal: J. B. Lippincott Company. London: Pitman Medical Publishing Co. Ltd. 1958.

The Principles of Electrophoresis. By René Audubert and Serge de Mende. Translated by A. J. Pomerans. (Pp. 142+viii; illustrated. 25s.) London: Hutchinson Scientific and Technical. 1959.

Electrophoresis. Theory, Methods, and Applications. Edited by Milan Bier. (Pp. 563+xx; illustrated. $15.) London: Academic Books Ltd. 1959.

Atti della Società Italiana di Cardiologia. XX Congresso, Rimini, 8-10 June 1958. Volume II. in 2 Parts. (Pp. 813; illustrated.) Rome: Editi a Cura della Segreteria della Società. 1958.

Oxygen and Allied Therapy. By Howard G. Lapsley. (Pp. 54. $2.) Plainfield, New Jersey: H. G. Lapsley. 1959.

Problèmes d'Organisation et de Fonctions chez les Bactéries et les Virus. Published under the direction of J. André Thomas. (Pp. 386+xii; illustrated. 5,000 fr.) Paris: Masson et Cie. 1958.

Wolff's Diseases of the Eye. Revised by Redmond J. H. Smith, D.O.(Eng.), M.S.(Lond.), F.R.C.S.(Eng.). Fifth edition. (Pp. 226 +x; illustrated. 42s.) London: Cassell. 1959.

BRITISH MEDICAL JOURNAL
LONDON
SATURDAY APRIL 25 1959

RADIATION AND LEUKAEMIA

The evidence that ionizing radiations may induce leukaemia in man has become increasingly convincing during the last fifteen years. Apart from analogy with the experimental production of leukaemia in irradiated animals, the evidence has been drawn from three chief fields of observation. First, the incidence of leukaemia among American radiologists in past years—before standards of protection from stray irradiation were as high as they are to-day—has been shown to exceed considerably that among their non-radiologist colleagues.[1 2] It is reasonable to connect this higher incidence with occupational exposure to *x* rays. Secondly, a sharp increase in the death rate from leukaemia has taken place among the survivors of the atomic-bomb attacks on Hiroshima and Nagasaki in August, 1945.[3] Thirdly, leukaemia has developed unduly often in certain groups of patients treated by intensive radiotherapy,[4] and perhaps also after diagnostic irradiation in foetal life, although the evidence for this is less clear cut.[5] A latent period of about 5 to 8 years usually preceded the clinical onset of disease, and the type of leukaemia has been predominantly acute, with the chronic myeloid form less common and chronic lymphatic very rare.

In all the reported cases in which irradiation has seemed a probable cause of later leukaemia the dose-rate of exposure has been high, ranging from about 20 r per minute to the enormous doses associated with nuclear explosions. At the same time the total doses to the haemopoietic marrow have never been less than 100 r and usually much more. The uncertainty whether a threshold for either dose-rate or total dose exists below which exposure will not induce leukaemia has permitted contradictory assessments of the leukaemogenic dangers of additional background radiation from nuclear-weapon tests.[6] Further, Dr. T. C. Carter, of Harwell, said at a conference of the Royal Statistical Society's medical section last week that the rate of mutation which possibly triggers off the disease might depend partly on the intensity of radiation and not only on the total dose.

A good deal remains to be learned about the mechanism by which radiation may induce leukaemia. A question commonly asked is whether the steady increase in the recorded mortality from leukaemia during the past thirty years in all countries for which figures are available might be attributable to increasing exposure of the general populations to ionizing radiations, especially to *x* rays used in medical diagnosis and treatment. A strong argument against this possibility has been that irradiation characteristically induces acute leukaemia or chronic myeloid leukaemia but not the chronic lymphatic form, whereas chronic lymphatic leukaemia has undoubtedly made up a large part of the overall increase. Moreover, if low rates of exposure from natural or artificial background radiation do in fact exert a cumulative leukaemogenic effect—a hypothesis not yet proved or disproved—the incidence of leukaemia induced in this way would be expected to rise with increasing age. But it is again chronic lymphatic leukaemia which shows such an age relationship most conspicuously.

The unsatisfactory classification of the varieties of leukaemia recommended in the *International List of Causes of Death* and used by many countries in compiling mortality figures has made it difficult in the past for statisticians to obtain clear data on death rates from different types of the disease. From information recently made available by the Registrar-General of England and Wales, Drs. W. M. Court Brown and R. Doll have now been able to study the death rates from the chief forms of leukaemia in relation to age over the period 1945 to 1957. Their conclusions, reported elsewhere in this issue (p. 1063), are that the apparent increase in the mortality from chronic lymphatic leukaemia and a large part of that attributed to other forms of leukaemia at ages over 60 are due to the better recognition of these diseases in the elderly, and that the observed increases in death rates from acute leukaemia at ages under 60 years are largely real and due to increasing exposure of the population to leukaemogenic factors in the environment. Court Brown and Doll have thus at least partially countered the arguments against attributing the increase in mortality from leukaemia to radiation exposure by showing that the increase in age groups above 60 is apparent rather than real, and that below this age the increase is due predominantly to acute leukaemia and to a small extent to chronic myeloid leukaemia—the forms of the disease which radiation is known to induce.

[1] March, H. C., *Amer. J. med. Sci.*, 1950, **220**, 282.
[2] Warren, S., *J. Amer. med. Ass.*, 1936, **102**, 464.
[3] Moloney, W. C., *New Engl. J. Med.*, 1955, **253**, 88.
[4] Court-Brown, W. M., and Doll, R., *Spec. Rep. Ser. med. Res. Coun. (London)*, No. 295, 1957, H.M.S.O., London.
[5] Stewart, Alice, *et al.*, *Brit. med. J.*, 1958, **1**, 1495.
[6] Finkel, M. P., *Science*, 1958, **128**, 637.

LUNG CANCER AND CONSTITUTION

It is possible that persons of a certain temperament are more likely to smoke tobacco than persons of a different temperament,[1] and the careful observations on Swedish twins discussed by Dr. Lars Friberg and his colleagues at p. 1090 of the *Journal* this week go some way to confirm this view. Of 59 monozygotic pairs 45, or 76%, had fairly similar smoking habits, while of the 59 dizygotic pairs only 34, or 58%, were alike. The difference is not very large, but is unlikely to be due to chance, and it is in keeping with the similar, though less precisely analysed, statistics of twins previously published by Sir R. Fisher.[2 3] As the Swedish authors point out, such a disparity might be due to a more uniform environment for the monozygotic than the dizygotic group and is not necessarily the result of a genetic factor. However that may be, even if the disparity was wholly genetic in origin, that fact would not weaken the evidence, derived from many investigations, associating cigarette smoking with lung cancer or the cause-and-effect interpretation of that association.[4]

The constitutional make-up of one person may make him more susceptible to the effects of an environmental factor, such as tobacco smoking, than another person with a different make-up. But then the environmental factor is still the operative agent; without it neither will succumb. Nor is there any evidence of hereditary factors in lung cancer, and from what we know of them in the other main forms of cancer in human beings they are not likely to be strong. The lack of evidence on inherited factors in lung cancer bears hardly on the thesis that there is a genetic constitution which includes a desire to smoke and a liability to lung cancer independent of the smoking. Moreover, there are several weighty counter-observations to the thesis. First, for instance, it cannot account for the great rise in mortality from the disease that has taken place in recent years. Some other environmental change must be postulated for that and one to which males are more exposed, or more sensitive, than females. The experimental evidence that tobacco tars contain agents carcinogenic to experimental animals[5] must be regarded as coincidental and unrelated to the epidemiological evidence in man. Secondly, the prospective inquiries carried out both in this country[6] and in the U.S.A.[7] have shown that a fall in mortality from lung cancer follows the giving up of smoking even after many years. Thirdly, the evidence for a causative association between lung cancer and cigarette smoking does not rest merely on a broad contrast between the death rates of smokers and non-smokers. It is derived from a gradient in mortality that rises steadily from non-smokers to regular heavy cigarette smokers, the latter having a death rate some 40 to 50 times as high as the former.

In short, while there may be an inherited element in the predisposition to smoke, no one has yet detected an inherited element in the liability to lung cancer and certainly not a genetic situation in which the predisposition to the one and the liability to the other are united. In addition to the important observations mentioned above for which the constitutional theory offers no satisfactory explanation, F. Edwards, T. McKeown, and A. G. W. Whitfield[8] have drawn attention to another type of observation which tells against it. They point out that "the common diseases with which smoking is so consistently associated are those in which an oral or respiratory irritant might be expected to be significant"—diseases in which smoking had been suggested on clinical grounds to have some harmful influence long before the statistical evidence of it. The conclusion reached by the Medical Research Council[4] has been amply confirmed by additional epidemiological evidence, in particular by the results of a third prospective inquiry in the U.S.A.[9] and by an exhaustive and admirably conducted retrospective study in France.[10–12] More recently it has been wholly supported by a group of workers in the U.S.A. who have carefully reviewed all the recent evidence on this subject and the criticisms of it that have been produced.[13] The final word to their study is as follows:

"If the findings had been made on a new agent, to which hundreds of millions of adults were not already addicted, and on one which did not support a large industry, skilled in the arts of mass persuasion, the evidence for the hazardous nature of the agent would be generally regarded as beyond dispute. In the light of all the evidence on tobacco, and after careful consideration of all the criticisms of this evidence that have been made, we find ourselves unable to agree with the proposition that cigarette smoking is a harmless habit with no important effects on health or longevity. The concern shown by medical and public health authorities with the increasing diffusion to ever younger groups of an agent that is a health hazard seems to us to be well founded."

[1] Heath, C. W., *A.M.A. Arch. intern. Med.*, 1958, **101**, 377.
[2] Fisher, R. A., *Nature (Lond.)*, 1958, **182**, 108.
[3] —— ibid., 1958, **182**, 596.
[4] Medical Research Council, *Brit. med. J.*, 1957, **1**, 1523.
[5] Wynder, E. L., ibid., 1959, **1**, 317.
[6] Doll, R., and Hill, A. B., ibid., 1956, **2**, 1071.
[7] Hammond, E. C., and Horn, D., *J. Amer. med. Ass.*, 1958, **166**, 1159, 1294.
[8] Edwards, F., McKeown, T., and Whitfield, A. G. W., *Lancet*, 1959, **1**, 196.
[9] Dorn, H., Seventh International Cancer Congress, London, 1958.
[10] Schwartz, D., and Denoix, P. F., *Sem. Hôp. Paris*, 1957, **33**, 3630.
[11] —— —— and Anguera, G., *Bull. Ass. franç. Cancer*, 1957, **44**, 336.
[12] Denoix, P. F., Schwartz, D., and Anguera, G., ibid., 1958, **45**, 1.
[13] Cornfield, J., *et al.*, *J. nat. Cancer Inst.*, 1959, **22**, 173.

EVOLUTION AND HISTORY

It was 100 years ago that Darwin's *Origin of Species* presented, with a wealth of detailed observation, the facts which established the theory of the evolution of species by natural selection. The logic on which his theory rests is inexorable, and its premises have been amply verified. Despite this, we have not yet attained a full understanding of any one evolutionary process. Still less are we able to assess with accuracy the contribution to evolution that a particular individual may make. In other words, we cannot predict all the consequences of allowing an individual, whether human, animal, or plant, to make its contribution to the posterity of its species through breeding. For these reasons, as well as for others, biologists nowadays would in general reject the arguments for socially enforced eugenic measures. The advocates and practitioners of genocide or of the sterilization of criminals are applying a naive conception of biology to a species whose natural history is only beginning to be understood.

As Professor L. Hogben said, at the recent Edinburgh conference on "Darwinism and the Study of Society," reported at p. 1111 of the *Journal* this week, the "social Darwinists" have got their biology wrong. It is not that Man can claim any special dispensation from natural law: he shows variability, much of it genetically determined or genetically conditioned. Moreover, human individuals may contribute much, little, or nothing to the genetical make-up of succeeding generations according to their viability and fertility, and human mating is a far from random process. While the possible consequences of these facts need examining in the light of experimental results obtained with animals, such study becomes meaningless if it ignores the unique biological and social features of our species. As Hogben said, man is uniquely educable, and transmits to the next generation not only his genes but his experience through speech and writing.

The participants at the Edinburgh conference were concerned both to assess the extent to which biological processes enter into man's social history and to uncover parallels between evolution and history that might shed light on social change. Evidently change in human history has different causes from change in the evolution of living organisms. Social change may owe something to the genetic variability of human populations, but there is no evidence that it is dependent on genetic change. Indeed, it is the salient characteristic of Man that his mental adaptability is joined to a system of communication by speech which permits the inheritance of acquired social experience. Though this may remove history from a close relationship with biology, not everyone would follow Professor B. Farrington to the extent to which he seemed to subordinate Man's biology to his social life. Even so, he provoked thought in saying that the "natural family" does not exist, and that human eating and defaecation are not so much acts of nature as methods of dealing with nature according to conventions and rules.

Part of the service that Darwin has performed for social study is that of encouragement, and historians may derive some help in their own studies from seeing how biologists have investigated the course of biological history, or evolution. It is only natural that the historian should be tempted to look for analogies. Analogy in this context may, as Professor Asa Briggs urged, be dangerous, or, as Mr. Maynard Smith thought, of little value, though this is perhaps a subject upon which it is well to avoid intellectual perfectionism. To act on an argument from analogy may be rash, but analogical thinking is doubtless a part of all thinking. We hardly speak or think without metaphor, nor need this worry us so long as we are conscious of it.

Thus Professor C. H. Waddington asked whether certain biological facts, such as the linkage of genes, had parallels in the observed grouping of social characteristics. In so doing he was not claiming anything like identity between biological and social inheritance, but, rather, encouraging his audience to wonder whether knowledge of one may lead to the discovery of something about the other. Though we may expect a philosophy of change to embrace both organic evolution and social history, we must admit that neither the biologists nor the historians are yet ready to produce it. The conference showed how important it is that they should be aware of each other's problems and achievements. And it is a tribute to Darwin's genius that 100 years later leading biologists, historians, and sociologists should be stimulated to consider his work and to draw inspiration from it.

DETACHMENT OF RETINA

The last decades have seen two major advances in eye surgery. Corneal grafting has had ample acclaim, and its problems have been aired on the stage, cinema screens, television, and even in Parliament. But the other great surgical triumph, that of mastering retinal detachment, has probably saved more eyes from blindness even than the perfection of corneal-grafting technique. The pioneering work in both of these fields by Professor Louis Paufique, of Lyons, is well known far outside the world of ophthalmology, and in electing

[1] See annotation, *Brit. med. J.*, 1958, 2, 1345.

him as Bowman lecturer for 1959 the Ophthalmological Society of the United Kingdom added its well-merited tribute.

For his Bowman lecture, delivered earlier this month in London, Professor Paufique reviewed the present status of the treatment of retinal detachment, first looking back to the days of his youth, before Gonin had performed his first successful repair by use of the Paquelin thermocautery. Even in 1929 Professor Gayet had declaimed, "To wish to treat a retinal detachment, one must be either a charlatan or a fool." After the uncertain results with the cautery came Weve's introduction of the safer and more reliable diathermy and improved methods of localizing the retinal tears by transillumination. In 1950 the more difficult and dangerous full-thickness resection of Muller and Lindner began to be replaced by lamellar scleral resection. This last operation has been elaborated, particularly by C. D. Shapland in England and Paufique himself in France, and nowadays is the operation of choice in about half the cases of detachment of retina. Still more recent advances have included the transplantation of vitreous and coagulation by light[1]: these procedures now have their established place in a small percentage of cases.

Reviewing his last 524 cases, Paufique recorded successful results in 70%—a figure which corresponds with most other recent assessments. In about half of the failures the nature of the detachment could be said almost to have precluded cure, but it is still difficult to find an adequate explanation for failure in the remaining 15%. Paufique therefore cast about for other factors in the pathogenesis of such detachments, and among the various possibilities he presented impressive histological evidence of certain congenital choroidal lesions which might well be responsible and so warrant prophylactic surgery. Discussing treatment, he stressed the value of the injection of lyophilized vitreous, which can readily be stored as a powder, and of coagulation by light. The place for preventive treatment, especially the use of epichoroidal galvanocautery, is still debatable.

RESPIRATORY PARALYSIS

The Wessex Regional Hospital Board came into being on April 1, and already has held at Portsmouth, on April 16, an instructive conference on poliomyelitis. The principal theme was the management of acute respiratory paralysis, and a series of speakers, physicians and anaesthetists, discussed the recognition of patients who are suitable for transfer to a centre for artificial respiration, the technique of transfer, and their care on arrival at the centre. Artificial respiration has become enormously more efficient since the development of centres with special interest in this problem. What made this possible was the discovery that a patient with respiratory weakness can be transferred to the centre with little risk provided he is under the care of an anaesthetist with experience of this type of work. The techniques for transporting such patients were reviewed at this conference by Dr. H. B. Sandiford, and in the main they are now well established. The principal difficulty is the administrative one of arranging for a team with the necessary experience to be quickly available whenever it is wanted. Though some regions are well served in this respect, perhaps not all are. Many disorders other than poliomyelitis can be successfully treated by artificial respiration. These include acute polyneuritis, tetanus, barbiturate poisoning, myasthenia gravis, and bronchitis with emphysema. The modern technique of artificial respiration is exacting, and, as Dr. J. M. K. Spalding emphasized, wasteful duplication is prevented and efficiency increased if, in any one area, all patients requiring artificial respiration from whatever cause are treated by the same medical and nursing team.

Many speakers stated that the extent of respiratory failure can easily be assessed clinically. It is fortunate if this is so, for the physician who has to summon help from the respiration centre may not have special equipment available for investigating the patient's respiratory ability in detail. A useful clinical test is to assess the vital capacity roughly by making the patient take a deep breath and count out loud as far as he can in one breath. The physician can get some idea of a normal response by himself performing the test. If a patient with a paralysing disease has a vital capacity one-third to one-quarter of normal, the need for artificial respiration must be seriously considered. Other danger signs are the need to take a breath in the middle of a sentence, restlessness, sleeplessness, and activity of the sternomastoids or alae nasi. Cyanosis and panting respiration indicate that respiratory failure has already occurred and treatment is urgent. Sedatives must never be given if respiratory deficiency is suspected. Professor E. A. Pask questioned reliance on clinical observation by stating—though his audience knew better than to believe him—that he was himself unable to assess a patient's respiratory ability clinically. But he clearly showed that, though clinical judgment can on occasion be at fault, in respiratory failure as in other problems it is exceedingly valuable. Special investigations are naturally also helpful for the particularly difficult case.

GAS CYSTS OF INTESTINE

Pneumatosis cystoides intestinalis is a rare disease which goes under a variety of other names, such as gas cysts of the intestine, pseudocystic disease of the intestine, and intestinal emphysema. In 1952 L. G. Koss[1] published a review of the 213 cases then reported in the world literature and found that they fell into three main groups. The majority showed disease of the small intestine; most of these had a lesion in the region of the gastric pylorus, usually a peptic ulcer of the stenosing type. A smaller group showed gas cysts of the caecum, which were thought to be secondary to disease of that organ or the appendix; and a few had cysts in the remainder of the colon.

The cysts themselves can be divided into two main types. In most patients they are subserosal, so that they are readily visible on inspection of the intestine at

laparotomy or necropsy. In others they are confined to the submucous layer and are not visible on external inspection of the intestine; they bulge into the lumen, so that they bear some resemblance to polyps. In both groups the cysts are thin-walled and contain gas; when pressure is applied to them they burst like small balloons. Rupture possibly occurs during life, because spontaneous pneumoperitoneum is sometimes present in this condition. The cysts usually do not communicate with one another, though there are some exceptions to this rule. For a variety of reasons, given by Koss, the cysts appear to be lymphatic vessels distended with gas. The gas is not air but is a mixture of nitrogen, oxygen, carbon dioxide, and hydrogen.

There are two main theories to account for their occurrence, the mechanical and the bacteriological. The mechanical theory holds that, in patients with peptic ulcer and some degree of pyloric obstruction, stomach gas is forced under pressure into lymphatics which have been opened by the ulcerating process and is then distributed further down the intestine by peristalsis. It is then necessary to postulate that in most cases the gas forms localized cystic spaces remote from the original lesion. That mechanical causes can be responsible is evident from the reports of cases with the sigmoid colon affected in which the condition followed sigmoidoscopic examination or removal of a polyp.[2-4] The bacteriological theory implies that gas is formed in the lymphatics by bacterial action. In hogs, in which pneumatosis intestinalis is much more common than in man, gas-forming organisms of the *Escherichia coli* group have been isolated by various observers. An objection sometimes advanced against the bacteriological hypothesis is that, though pneumoperitoneum is a frequent accompaniment of gas cysts, peritonitis is rare; but this argument is not necessarily valid.

The clinical course is very variable. In many cases the condition is found by chance at laparotomy or necropsy. In others the condition has been observed to disappear spontaneously. In a few there are serious clinical effects, especially chronic diarrhoea, sometimes with blood and mucus in the motions, and occasionally the malabsorption syndrome. If the symptoms are troublesome and the disease is localized, resection of the affected portion of bowel can be carried out, and this usually gives relief. In the majority of cases, when the condition is associated with a lesion such as peptic ulcer, the supposed "primary" lesion is best treated before considering resection of the affected intestine.

In the past it has been thought difficult to diagnose the condition in life, but the radiological appearances on barium follow-through or enema examinations are characteristic and can be recognized by those familiar with the condition. The barium column is indented with multiple gas pockets, resembling translucent polyps.[5-7] In the unusual variety when the cysts are present in the terminal colon they can be diagnosed on sigmoidoscopy.[8] If a biopsy specimen of cyst is taken during sigmoidoscopy, the cyst is likely to be deflated and the diagnosis is then certain.

[1] Koss, L. G., *Arch. Path.* (*Chicago*), 1952, **53**, 523.
[2] Marshak, R. H., Lipsay, J. J., and Friedman, A. I., *J. Amer. med. Ass.*, 1952, **148**, 1416.
[3] —— Blum, S. D., and Eliasoph, J., ibid., 1956, **161**, 1626.
[4] Sedgwick, C. E., and Ruddell, K. S., *Lahey Clin. Bull.*, 1954, **8**, 238.
[5] Benson, R. E., and Raitt, G. P., *Ann. Surg.*, 1956, **144**, 907.
[6] McGee, A. R., Penny, S. P., and Williamson, N. L., *Radiology*, 1956, **66**, 88.
[7] Creevey, K., Cohen, J. L., and Riley, G. J., *New Engl. J. Med.*, 1958, **259**, 912.
[8] Pemberton, H. W., Smith, W. G., and Holman, C. B., *Amer. J. Surg.*, 1957, **94**, 472.

GOOD FOOD IN HOSPITALS

There may be a few hospitals dotted about Britain where, owing to the genius of some member of the staff, the food which reaches the patient's plate would win approving remarks in the *Good Food Guide*. But if commercial caterers find it so difficult to reach this standard, how much more difficult is it for hospitals. In a memorandum[1] on hospital diets published by the King Edward's Hospital Fund for London there is a chapter on catering in mental hospitals describing conditions which would take the stuffing out of the most highly trained *hôtelier*. Up to 2,000 patients, all feeding at approximately the same time, have three cooked meals a day. The food is prepared in huge old-fashioned kitchens, where the most noticeable items of equipment are 100-gallon boiling-pans and where it is a longish walk from cooking-stove to scullery. These conditions naturally repel suitable applicants for vacancies on the kitchen staff and consequently there is a great shortage of skilled cooks. The removal of the food from the kitchen to the patient's villas and wards is a major operation, demanding a fleet of forty or more food trolleys. Until the trolleys are loaded the cooked food has often to be kept on the kitchen floor. Having reached the villa, the containers have then to be taken from the trolley and carried up three flights of stairs to the wards on the top floors, lifts being unknown in the older hospitals.

General hospitals for the most part have a slightly easier task, but here again the structural inadequacy of kitchens and shortage of staff are serious handicaps. In his foreword to the King's Fund memorandum Dr. F. Avery Jones remarks, "The existence of national salary scales has an obvious administrative appeal but results in inflexibility when dealing with local special conditions and also makes it impossible to recognize outstanding flair and skill." This is a crucial difficulty, for the memorandum emphasizes that the many defects in hospital catering can be overcome "only by the appointment of fully qualified and experienced men and women as heads of hospital catering departments, with responsibilities that enable them to fulfil their duties properly."

The memorandum, which is a booklet of over 60 pages, is full of practical advice which should help hospitals to serve the best meals possible in the circumstances. The trouble is the circumstances are often so incompatible with good catering that only radical and expensive structural alterations can help to put things right. The King's Fund memorandum gives strong support to Mr. Lawrence Abel and Mr. Walpole Lewin's demand[2] for a substantial increase in the capital allocation for the hospital service.

[1] *Third Memorandum on Hospital Diet*, 1959. Obtainable from King Edward's Hospital Fund for London, 34, King Street, London, E.C.2. Price 2s., post free.
[2] Abel, A. L., and Lewin, W., "Report on Hospital Building," *Brit. med. J., Supplement*, 1959, **1**, 109.

IMPERIAL CANCER RESEARCH FUND

The Imperial Cancer Research Fund is planning a large expansion of its work, and the building of new laboratories in Lincoln's Inn Fields has already started. Dr. G. F. Marrian, F.R.S., will take up his duties as director of research later this year, and in a foreword to the fifty-sixth annual report of the Fund he has described how the research work is to be developed. The laboratories will be organized into divisions. The director will be in charge of the division of chemistry and biochemistry, Dr. R. J. C. Harris of the division of experimental biology and virology, Dr. A. R. Currie of the division of pathology, Mr. P. C. Williams of the division of physiology and endocrinology, and Dr. C. C. Spicer of the division of statistics. This divisional basis of organization is necessary for administrative convenience, but, as Dr. Marrian writes, in practice most of the research problems will be studied co-operatively, "since with few exceptions they are likely to require the skills of more than one scientific discipline for their solution."

The lines which future research may take cannot be forecast, but Dr. Marrian suggests that the study of tumour viruses will almost certainly be pressed forward at the Mill Hill laboratories of the Fund, while in the new buildings in Lincoln's Inn Fields the main emphasis is likely to be on research on hormone-dependent tumours, as it is at present in the existing laboratories. Of this present research Professor G. Hadfield gives an encouraging and clear account elsewhere in the report.

PUBLIC HEALTH SERVICE REMUNERATION

The new salary scales for local authority medical officers recommended by Committee C of the Medical Whitley Council[1] are published in this week's *Supplement*. Increases vary from 9.2% over present minimum scales to 18.3% over present maximum scales. In round figures, maximum possible salaries for medical officers of health will range from £2,465 for a medical officer to a population group of up to 75,000 to £4,010 for a M.O.H. to a population group of from 400,001 to 600,000. For population groups over 600,000 the salary, as at present, is discretionary. Senior medical officers and assistant medical officers will have maxima of £2,200 and £1,640 respectively. Divisional medical officers will be on the same scale as senior medical officers, but the additions to their salary related to size of population will be increased. Deputy medical officers will receive two-thirds of minimum salary and two-thirds of the increments of their medical officer of health. Committee C's circular to local authorities reminds them that they may create posts intermediate between assistant medical officer and senior medical officer, and use of this discretion should help those in the junior grade whose lot, though much improved, is not entirely happy. The recommendations apply to Scotland as well as England and Wales.

[1] Whitley Councils for the Health Services, M.D.C. Circular No. 42.

TOP SURGEONS

A photograph in a Sunday newspaper a few weeks ago showed the President and the Council of the Royal College of Surgeons of England (and others) listening to the Hunterian Oration. Leaning forward earnestly from a solitary column of type was the orator himself. The names of those in the two front rows were given in full so the reader should be in no doubt as to their identity. Not long after this, gossip-column writers described with glee a party in Lincoln's Inn Fields where stars of the *Emergency Ward 10* film drank cocktails with the College's famous skeletons. Photographs again. As the President of the College of Surgeons is the most unassuming and modest of men, it was obvious there must be something desperately wrong with the present state of the College for him to assent to this kind of publicity. Like many a private doctor suspected of advertising, it wanted, and wants, money—and apparently quite a lot. The College deserves it. It is a national institution built up by the labours of famous men. But many national appeals for money have been launched before this without attempts to publicize the persons behind the cause of the appeal. The College of Surgeons could probably raise the money it wants without losing its dignity and without giving publicity to the members of its council. No one could have felt at all happy at seeing the full-page advertisement in last week's *New Statesman* and *Spectator* announcing the presentation by "Granada" on I.T.V. of SURGEON—printing the names of the President and six members of the College Council (two of them also members of the B.M.A. Council), complete with degrees, diplomas, orders, and honours. And then, last Sunday, a picture in a Sunday newspaper of a rather perplexed P.R.C.S. rehearsing for this Thursday's show.

This *Journal* has a great respect for the present President of the Royal College of Surgeons of England. No one who knows him can doubt that his first concern is for his college and the last is for himself. He is not in private practice, and therefore does not stand to gain any professional advantage from the present series of publicity stunts of which he is the unwitting centre-piece. Doubtless they are as distasteful to him as they may be pleasing to the ingenious minds which have thought them up. We hope the College will raise the money it needs. We hope, too, that the President will look a bit more critically at the advice he is receiving from the promoters of the various schemes for raising it. It would be a pity if the College, in achieving its target of £3m., found that in the process it had lost something more precious than money.

PRINTING THE JOURNAL

There is a dispute between the printing trade unions and the master printers. Until the dispute is settled it looks as if the customary excellent service from its printers which this *Journal* enjoys may be interrupted. If overtime is banned we shall have to go to press earlier than usual. We much regret the inconvenience that may be caused to readers.

Clinicopathological Conference

A CASE OF CHRONIC TUBERCULOSIS

DEMONSTRATED AT THE

POSTGRADUATE MEDICAL SCHOOL OF LONDON

This is the case of a young man with disseminated tuberculosis who ultimately died of chronic renal failure (Case No. 80,761 ; P.M. No. 8,407).

Clinical History

Dr. J. G. SCADDING: This patient was born in 1926. He was first admitted to Hammersmith Hospital in October, 1947, and died there 10½ years later. In childhood he had had otitis media, mumps, measles, whooping-cough, and scarlet fever. At the age of 13 he had rheumatic fever and was in hospital for three months. At the age of 17 he had acute nephritis, which followed a sore throat. He had haematuria and oedema of the face and ankles at the beginning of this illness. In the acute stage the blood urea rose to 72 mg./100 ml. The albuminuria persisted for a long time and led to his staying six months in hospital, but it cleared at the end of this time. In November, 1946, at the age of 20, he had a lymphocytic meningitis with right hemiparesis. This gradually cleared up during a two months' stay in hospital. Two weeks after transfer to a convalescent hospital he developed pain in the chest, headache, and weakness of the right arm. This also cleared up gradually, but a chest radiograph in April, 1947, when he had another febrile episode, showed consolidation of the left lower lobe (Fig. 1). Repeated examinations of the sputum at this time were negative for tubercle bacilli. The leucocyte count and sedimentation rate were persistently raised. It was for the investigation of this unexplained consolidation that he was admitted in October to Hammersmith Hospital for the first time.

FIRST ADMISSION

At this time (October, 1947) he was thin and pale, with variable pyrexia and a cough producing 15 to 30 ml. of mucopurulent sputum daily. The chest radiograph showed persistent consolidation of the left lower lobe. Bronchoscopy showed widespread acute inflammatory change in the bronchi, more especially in the left lower lobe bronchus. Biopsy of this bronchus showed infiltration of the mucosa with polymorph neutrophils. Aspirated secretions were examined for tubercle bacilli with negative results. A tuberculin jelly test was briskly positive.

In December, 1947, tubercle bacilli were found in the sputum for the first time by guinea-pig inoculation, and subsequently several cultures of the sputum for tubercle bacilli were positive. In January, 1948, he developed headache, vomiting, neck stiffness, and papilloedema. Lumbar puncture showed clear cerebrospinal fluid under increased pressure, with normal protein content and 15 lymphocytes per cubic mm. This episode of "meningism" subsided without specific treatment.

Between May and September, 1948, destructive tuberculous changes in bone developed in the right ulna (Fig. 3) (with a cold abscess), behind the right mastoid process (with a cold abscess), in the neck of the right humerus, in the right clavicle, in several cervical vertebrae (with a paravertebral abscess, Fig. 2), in the right side of the mandible, in the left tibia, and finally in the left tarsus. By this time streptomycin had become available, and he received 1 g. daily up to a total of 98 g. The left foot was immobilized in plaster. The bone lesions all resolved satisfactorily, and in April, 1949, he was discharged to the Brompton Hospital Sanatorium, Frimley.

SUBSEQUENT COURSE

In July, 1949, he was readmitted to Hammersmith Hospital because of the discovery of persistent albuminuria, amounting to about 1 g. daily. Nothing significant was found in the urinary deposit. The blood urea was 43 mg./100 ml. and the urea clearance 100%. An intravenous pyelogram was normal. No tubercle bacilli were found in repeated cultures of the urine. A biopsy of his gums showed no evidence of amyloid. He was treated with a further 69 g. of streptomycin, and albuminuria had ceased by the time of his discharge in December, 1949.

He was admitted for the third time in June, 1950, because of diarrhoea and vomiting for one month and fever with left pleural pain for seven days. The lower lobe of the left lung was found to be consolidated. This did not respond to penicillin, and was presumed to be tuberculous, although tubercle bacilli were not found. Albuminuria was again found, amounting to 1.5%. The blood urea ranged between 50 and 75 mg./100 ml. Streptomycin in normal dosage produced toxic effects, the blood level 24 hours after a dose of 1 g. being 25 μg./ml. Effective blood levels were maintained with 0.25 g. every three days. The consolidation gradually resolved and he was discharged in November, 1950. There was no further activity of the bone lesions ; the left tarsus had healed with ankylosis of the mid-tarsal joints. He undertook training and obtained work as a watch repairer until July, 1952, when he had to stop because of tiredness. In September, 1952, oedema of the feet appeared for the first time.

He was admitted for the fourth time in October, 1952. Heavy albuminuria persisted. The blood pressure remained low, at 100/70 mm. Hg. The blood urea had risen to 188 mg./100 ml. Tubercle bacilli were once more isolated from the sputum on culture, and radiologically there was evidence of fresh consolidation in the middle zone of the left lung. Dull red papules appeared on the elbows, knees, and legs, and on biopsy proved to contain caseating tubercles. He was treated with streptomycin 0.25 g. twice weekly and isoniazid 200 mg. daily, and improved slowly, the consolidation gradually resolving and the blood urea falling to 88 mg./100 ml. He was discharged in March, 1953.

TERMINAL ILLNESS

After this he remained reasonably well until September, 1957, when he developed intermittent fever, tiredness, sore throat, thirst, loss of weight, and occasional

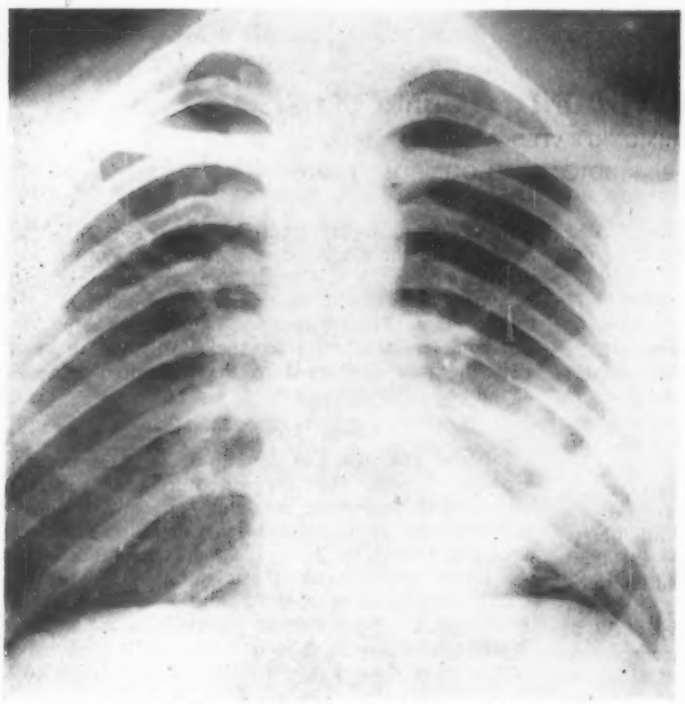


FIG. 1.—Chest radiograph (1947) showing left lower lobe consolidation.

vomiting and diarrhoea. He was now aged 31. At the end of December, 1957, he developed pain in the chest, cough, and frontal headache. He was admitted for the last time in January, 1958, thin, ill, and with persistent low fever. The blood pressure was 105/60 mm. Hg. On admission there was clinical and radiographic evidence of consolidation of the right lower lobe. This was apparently pneumococcal in origin and responded well to penicillin. Many cultures of the sputum for tubercle bacilli were negative. The blood urea on admission was 290 mg./100 ml. There was heavy albuminuria and hypoproteinaemia. His general course was steadily downhill, with persistent fever, anaemia, hypotension, and looseness of the bowels. A variety of therapeutic measures was tried ineffectively. On March 22 there was a sudden increase in the daily urinary output of albumin from 5 g. to 17 g., and, after this, very gross oedema developed and his downhill course was accelerated. He died in coma on May 4, 1958.

Clinical Diagnosis

(1) Chronic disseminated tuberculosis involving lungs, bones, brain, and skin, probably healed.

(2) Chronic renal failure, probably due to amyloidosis but possibly to chronic glomerulonephritis.

(3) Possibly renal vein thrombosis.

Post-mortem Findings

Professor C. V. HARRISON: This was a tall, thin young man, of height 6 ft. 1 in. (1.8 m.) and weight 10 st. 10 lb. (68 kg.), with pitting oedema of the lower limbs.

Respiratory System.—In the upper part of the anterior and lateral basal segments of the left lower lobe there was old fibrosis but no cavities or caseation. There was a little mild bronchiectasis. In the right lower lobe and left upper lobe there was some terminal bronchopneumonia. Apart from these two lesions, the lung parenchyma was normal. The two pleural cavities were obliterated by old fibrous adhesions. Histological examination of the left lower lobe showed peribronchial scarring (Fig. 4) with some destruction of alveolar tissue, but there was no sign of any active lesion.

Skeleton.—The right ulna showed a small depression at the site of the old osteomyelitis but no active lesion.

Urinary System.—The kidneys were shrunken, weighing 100 g. each (normally 150 g.). The capsules were adherent and the surfaces were finely granular. The cut surface showed narrowing of the cortex and loss of pattern. Iodine tests were strongly positive. The whole appearance was that of amyloid shrunken kidney. The renal arteries and their dissectable branches were normal. The right renal vein and its tributaries were normal. On the left side the renal vein from the upper half of the kidney was totally occluded by old thrombosis, and there was more recent, non-occluding thrombus in the distal part of the main

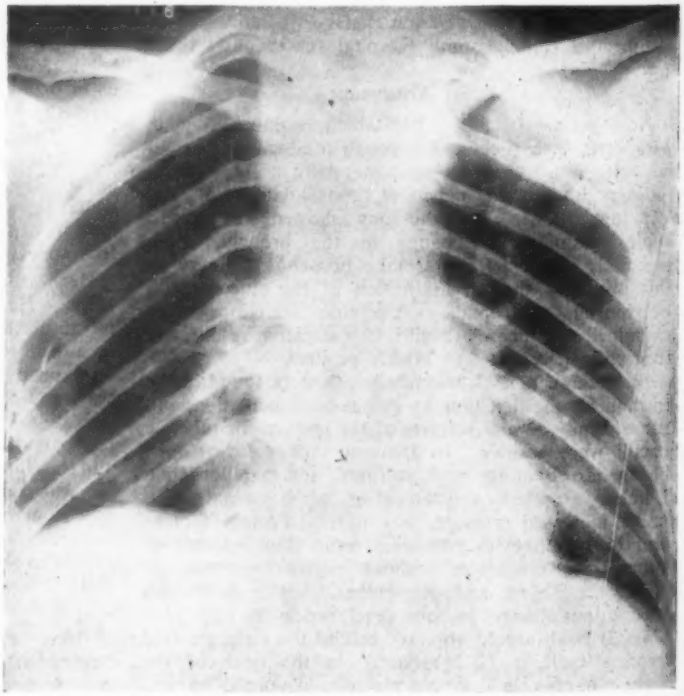


FIG. 2.—Chest radiograph (1948) showing the paravertebral abscess.

vei
thr
wit
of
was
(Fig
of
seq
atr
am
bas
art

was
the
aor
car
The
ism
spl
dou
not
app

nor
cul

sev
the
the
(Fig

app
test
mic
men

FIG.

vein. On histological examination (Fig. 5) the renal vein thrombosis was entirely organized and was consistent with a six-weeks history. Microscopically the diagnosis of amyloid shrunken kidney was confirmed. There was severe amyloid disease affecting every glomerulus (Fig. 6) and obstructing the blood flow through many of them. There was consequent widespread tubular atrophy. There were also amyloid deposits in the tubular basement membrane and in the arterioles.

Heart and Spleen.—There was a nodule of calcification in the left coronary cusp of the aortic valve and some endocardial scarring just below it. There was no sign of rheumatism and no cor pulmonale. The spleen (355 g.) was a little over double normal weight but did not show any characteristic appearance.

Brain. — This appeared normal. No sign of old tuberculosis could be found.

Suprarenals.—These showed severe amyloid disease affecting the inner three-quarters of the cortex. This was confirmed histologically (Fig. 7).

Other Organs.—Macroscopically the other organs appeared healthy and failed to show amyloid on testing with iodine, but amyloid was demonstrated microscopically at the following sites: thyroid basement membrane; pituitary basement membranes; and arterioles in the liver, spleen, pancreas (Fig. 8), intestine, heart, and parathyroid.

Pathologist's Diagnosis

(1) Healed pulmonary tuberculosis.
(2) Healed bony tuberculosis.

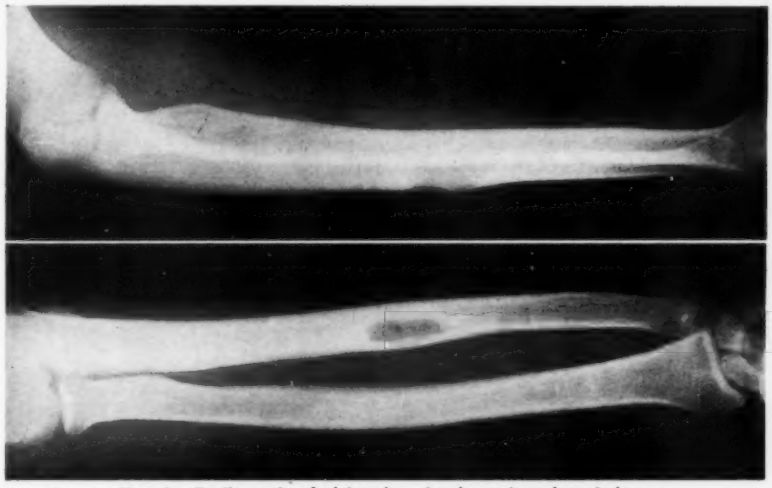


FIG. 3.—Radiograph of right ulna showing tuberculous lesion.

(3) Amyloid shrunken kidneys.
(4) Renal vein thrombosis.

Professor HARRISON: I have reviewed the post-mortem cases of amyloid disease seen at Hammersmith Hospital between June, 1946, and June, 1958. In the 4,704 necropsies during this period there were 50 examples of amyloid disease. The associated diseases were

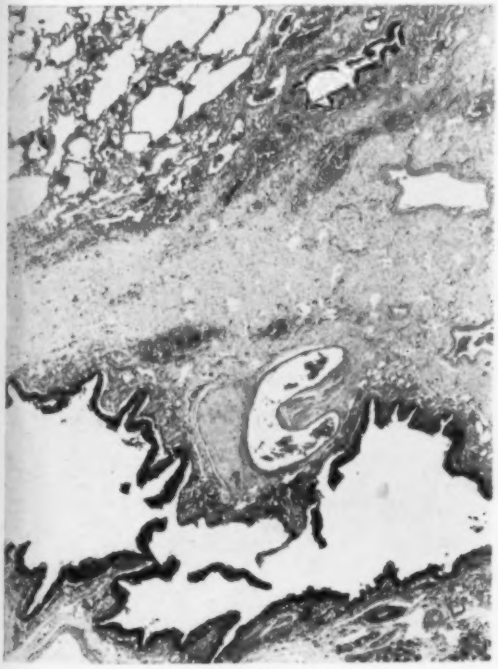


FIG. 4

FIG. 5

FIG. 4.—Peribronchial fibrosis in left lower lobe. (×24.) FIG. 5.—Left renal vein showing total occlusion by an organized thrombus. (×70.) The cut in the wall of the vein at the top of the picture was made when the vein was first examined.

tuberculosis in 19, sepsis in 12, rheumatoid arthritis in 10, and myelomatosis in 2. The amyloidosis was primary in 7.

Amyloidosis caused death in 18 out of the 50 cases; 17 died of uraemia and one of myocardial failure. Renal amyloidosis was present in 45 cases, and of these 11 had amyloid shrunken kidneys and 12 had renal vein thrombosis; 8 of the latter were recognized after 1956.

Discussion

Dr. SCADDING: It is very gratifying to have such complete pathological confirmation of our clinical views on this case. The only additional point on which we would have liked information concerns the central nervous system. We hoped that you might have found evidence of some residue of tuberculosis somewhere in the brain.

Professor HARRISON: I am afraid we did not. The brain was fixed in formalin. It was sliced up quite finely, but we failed to find any lesion. I think this may still have been a technical failure to spot a lesion only 1 or 2 mm. in diameter. We can say positively that there was no thickening or scarring in the meninges.

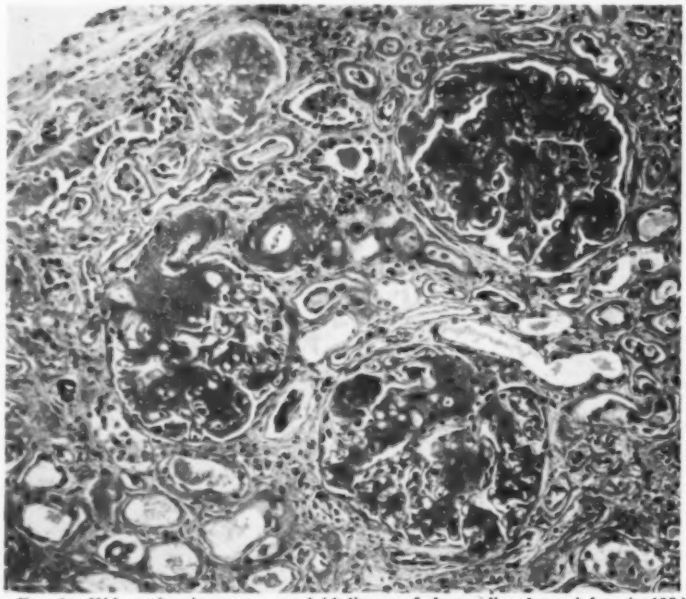


FIG. 6.—Kidney showing severe amyloid disease of glomeruli and arterioles. (×108.)

Dr. SCADDING: Seeing how well the bone lesions resolved, it is possible that a lesion in the central nervous system which had not led to too much caseation might have resolved to such an extent as to leave quite an insignificant scar. We thought that the episodes of lymphocytic meningitis were tuberculous in origin, and this hypothesis remains tenable.

Professor HARRISON: If I may take the analogy of searching for tuberculomata in children with meningitis, and knowing how very difficult they are to find, I think it is perfectly reasonable to postulate that this man may well have had a minute scar which we missed.

Dr. SCADDING: The tuberculosis in this case was of a very unusual chronic disseminated type. Presumably the bone lesions arose from haematogenous dissemination. I rather fancy that in the lungs you showed some vascular lesions in a healed stage, which might in their acute stage have been a source of haematogenous dissemination of tubercle bacilli. Where you showed the interrupted internal elastic lamina of one of those vessels might well have been the site of invasion by a caseating process.

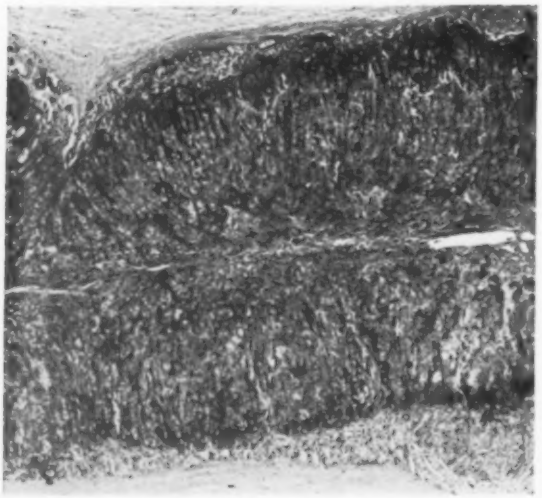


FIG. 7

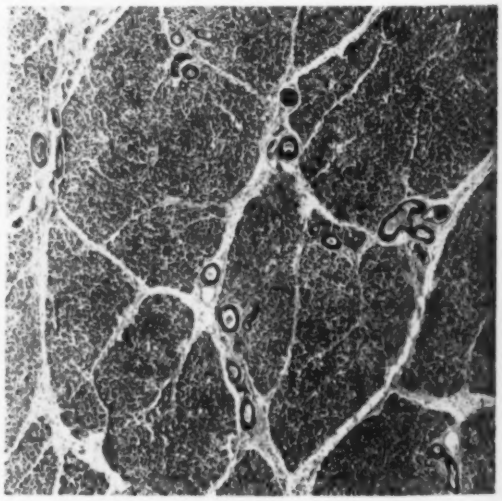


FIG. 8

FIG. 7.—Adrenal gland showing a darkly stained deposit of amyloid in the inner zones. (×24.) The pale subcapsular zones at the upper and lower limits of the photograph are not involved. FIG. 8.—Pancreas, showing amyloidosis of the arteries as darkly stained rings. (×24.)

tuberculosis in 19, sepsis in 12, rheumatoid arthritis in 10, and myelomatosis in 2. The amyloidosis was primary in 7.

Amyloidosis caused death in 18 out of the 50 cases; 17 died of uraemia and one of myocardial failure. Renal amyloidosis was present in 45 cases, and of these 11 had amyloid shrunken kidneys and 12 had renal vein thrombosis; 8 of the latter were recognized after 1956.

Discussion

Dr. SCADDING: It is very gratifying to have such complete pathological confirmation of our clinical views on this case. The only additional point on which we would have liked information concerns the central nervous system. We hoped that you might have found evidence of some residue of tuberculosis somewhere in the brain.

Professor HARRISON: I am afraid we did not. The brain was fixed in formalin. It was sliced up quite finely, but we failed to find any lesion. I think this may still have been a technical failure to spot a lesion only 1 or 2 mm. in diameter. We can say positively that there was no thickening or scarring in the meninges.

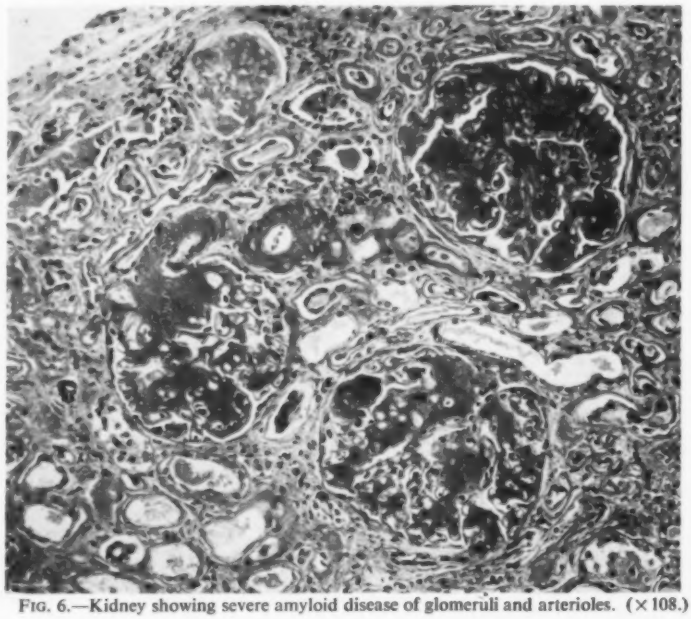


FIG. 6.—Kidney showing severe amyloid disease of glomeruli and arterioles. (×108.)

Dr. SCADDING: Seeing how well the bone lesions resolved, it is possible that a lesion in the central nervous system which had not led to too much caseation might have resolved to such an extent as to leave quite an insignificant scar. We thought that the episodes of lymphocytic meningitis were tuberculous in origin, and this hypothesis remains tenable.

Professor HARRISON: If I may take the analogy of searching for tuberculomata in children with meningitis, and knowing how very difficult they are to find, I think it is perfectly reasonable to postulate that this man may well have had a minute scar which we missed.

Dr. SCADDING: The tuberculosis in this case was of a very unusual chronic disseminated type. Presumably the bone lesions arose from haematogenous dissemination. I rather fancy that in the lungs you showed some vascular lesions in a healed stage, which might in their acute stage have been a source of haematogenous dissemination of tubercle bacilli. Where you showed the interrupted internal elastic lamina of one of those vessels might well have been the site of invasion by a caseating process.

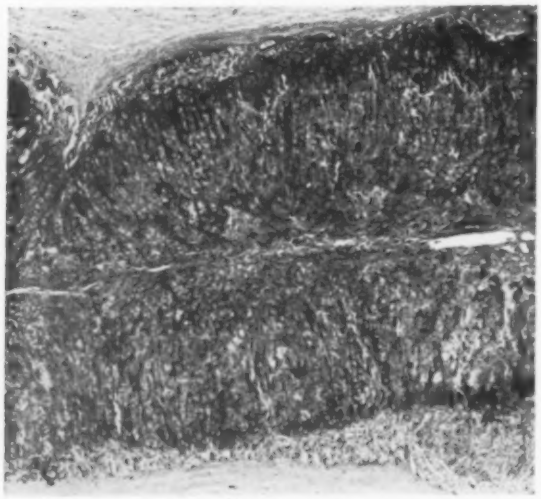


FIG. 7

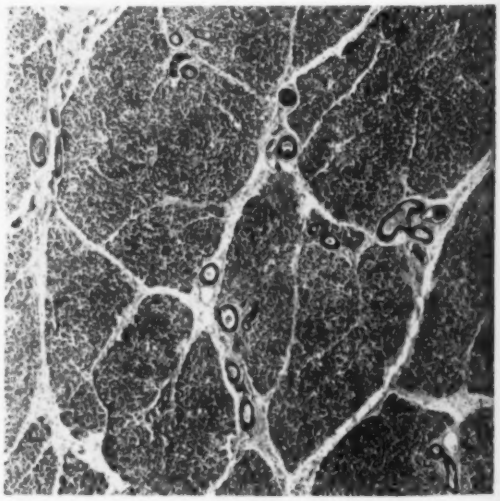


FIG. 8

FIG. 7.—Adrenal gland showing a darkly stained deposit of amyloid in the inner zones. (×24.) The pale subcapsular zones at the upper and lower limits of the photograph are not involved. FIG. 8.—Pancreas, showing amyloidosis of the arteries as darkly stained rings. (×24.)

Profe
Dr. S
really q
lung ch
any str
treatmen
consider
complete
the rena

The
amyloid
were co
and car
possible
positive
gave him

The l
to the k
seen se
develope
way to
tissues,
negative,
This ma
life. If
involve
test is li
renal bi
would li
this case

Dr. M
statistics
they sho
unless y
or actua
is the gr
series an
that man
last five
thrombo
the prev
explanati
simply th
venous s
top to t
venous r
they are
missed.
of only

In ma
clinically
amyloido
the time
have pro
thrombos
side first
spot it cl
a very se
patient us
is, of cou
pre-existi
the renal
renal fail
available

E

Professor HARRISON: That seems quite reasonable.

Dr. SCADDING: The degree of healing in this case was really quite remarkable. You will remember that the lung changes had resolved a good deal before we had any streptomycin to give him, and that he received treatment with streptomycin alone, which we should now consider quite inadequate. He in fact effected a complete recovery from his tuberculosis, and it was the renal lesion which was the cause of death.

The extensive involvement of the adrenals by amyloidosis is of interest. During his final illness we were concerned about the extreme degree of hypotension, and carried out such tests of adrenal function as were possible in a patient with renal failure. These gave no positive indication of depression of function. We even gave him cortisone without any effect on the hypotension.

The localization of the amyloidosis so predominantly to the kidneys is also of considerable interest. I have seen several other patients with tuberculosis who developed amyloidosis localized in the most remarkable way to the kidneys. Biopsies on the more accessible tissues, such as the gums and liver, were completely negative, although the kidneys were fatally involved. This made it difficult to arrive at a positive diagnosis in life. If the amyloidosis is so localized and doesn't involve massive organs like the liver, the Congo red test is likely to be negative, and nothing short of a renal biopsy will give the answer. Perhaps Dr. Milne would like to say something about the renal aspects of this case.

RENAL VEIN THROMBOSIS

Dr. M. D. MILNE: I thought Professor Harrison's statistics were extraordinarily interesting, though chiefly they show how fallacious post-mortem statistics can be unless you yourself are actually doing the necropsies or actually studying them. The most interesting fact is the gross disparity between the first seven years of this series and the last five years. His figures seemed to show that many of the cases of renal amyloidosis seen in the last five years had been complicated by renal vein thrombosis, and almost none had this complication in the previous seven years. Well, I do not think the explanation is that the incidence has changed. It is simply that in the last five years the whole of the renal venous system has been sliced up and looked at from top to toe. Usually these lesions are in the smaller venous radicals, interlobar and interlobular veins, and if they are not being looked for very carefully they are missed. Previously the biggest series gave an incidence of only 10%, whereas the proportion here is far higher.

In many ways this case was somewhat atypical clinically because the usual way in which renal amyloidosis presents with renal vein thrombosis is at the time when the kidneys are large, before they have progressed to amyloid shrunken kidneys. The thrombosis is usually bilateral. I suppose it starts in one side first and then spreads to the other, but you don't spot it clinically until both sides are affected. There is a very severe oliguria which resists treatment, and the patient usually dies in acute oliguric renal failure. This is, of course, one example of an acute exacerbation of pre-existing renal disease. In the present case, obviously, the renal vein thrombosis could not have influenced the renal failure very much because only a quarter of the available renal tissue was involved, though quite probably the clinical manifestation here was the increase of proteinuria from the damaged renal segment and the consequent increase of oedema. It just shows that a complication which is not described in the standard textbooks of pathology or clinical medicine can, in fact, be very important.

IS AMYLOIDOSIS REVERSIBLE?

Professor T. RUSSELL FRASER: There is one other point about the amyloidosis in this patient which I should like to raise. I think it may often have important practical issues. In the early stages, when he was readmitted because of his albuminuria (July, 1949), what could have been done to try and get rid of the amyloid? Is there any difference in the treatment at that stage that you would recommend now?

Dr. MILNE: I would say that amyloid is only reversible if it is spotted in the stage before there is any secondary fibroid contraction—as there was in these kidneys—that is, when the kidneys are very large and the only abnormality is leakage of protein with or without the nephrotic syndrome; before, in other words, they have produced azotaemia. The main practical point is that if you can remove the primary cause the amyloidosis is reversible and you will prevent progression to renal failure. Unfortunately in most cases the primary cause is not reversible. This patient had the best anti-tuberculosis therapy available at the time, and I don't suppose it would have made very much difference if he had had the present dosage. In patients with rheumatoid arthritis we still cannot clear up the primary disease. The one brilliant exception is sepsis, and here the prognosis has been improved by antibiotics and advances in surgery. Occasionally the course of the disease can be altered only by radical surgery. I should certainly say that, if you have a case of secondary amyloidosis complicating chronic osteomyelitis, say, of a leg, this is a strong indication for immediate radical cure by amputation. An early diagnosis of renal amyloid may therefore be of great practical importance, and this to me is one of the main indications for percutaneous renal biopsy in practical therapeutics. I am not talking now of research, but of practical therapeutics where an investigation is really going to influence your course of action.

Professor RUSSELL FRASER: What about the place of cortisone after you have dealt with the infection in the bone?

Dr. MILNE: I have a wonderful series of slides from a man with rheumatoid arthritis and controlled tuberculosis who was given cortisone. The proteinuria disappeared; his oedema disappeared; his liver shrank up till you could no longer feel it; he was a very satisfied client. But at the end of all that, biopsies of both the liver and kidneys showed no change in the amount of amyloid they contained. I don't think cortisone greatly influences this condition. He had about three years' cortisone therapy without improvement.

Professor RUSSELL FRASER: Of course, the trouble is one doesn't know what might have happened if he hadn't had the cortisone.

Dr. SCADDING: The other group of cases of amyloidosis in which surgical treatment can give very good results are those secondary to tuberculous empyemata. In these, radical surgery can result in complete disappearance of all clinical evidence of early

amyloidosis. One such patient whom I have followed up for some years seems to be remaining quite well. As Dr. Milne said, surgery has to be done before there is any irreversible fibrous change, before the kidney has started contracting.

WHY NOT GLOMERULONEPHRITIS ?

There is another point about the kidneys I would like to put to Dr. Milne. The earliest evidence of progressive renal disease was albuminuria, at first of slight degree, with increasing nitrogen retention. There was no oedema at this stage. This made us incline at first to the view that the albuminuria was due to a chronic stage supervening on the acute glomerulonephritis which he had suffered at the age of 17. Later, of course, the picture changed.

Dr. MILNE: I would say the two things go together. The cases with slight proteinuria usually don't have oedema, the cases with heavy proteinuria will tend to. The main point against a diagnosis of glomerulonephritis was the fact that he had a long period when he was free from proteinuria, and I think glomerulonephritis can therefore be excluded as a cause of the renal failure. If you can say that for many months or years after acute glomerulonephritis a patient has been consistently protein-free, that acute glomerulonephritis has healed. Any future renal failure has nothing to do with it.

Professor HARRISON: I just want to ask whether it is possible to have renal failure from chronic glomerulonephritis without hypertension.

Dr. MILNE: Most unusual.

Professor HARRISON: But possible ?

Dr. MILNE: I should think just possible, but most unusual.

INTESTINAL AMYLOIDOSIS

Dr. SCADDING: The latter part of this patient's story was marked by episodes of looseness of the bowels amounting sometimes to diarrhoea, and we wondered whether this might have been due to amyloidosis involving the intestine. Was there any evidence of that ?

Professor HARRISON: Yes, but only in the vasculature of the intestine. The vessels were quite extensively involved.

Dr. SCADDING: Probably not likely to give rise to diarrhoea and vomiting ?

Professor HARRISON: I am not so sure, because when we get this story of loose bowels in a patient with amyloid we pretty consistently do get vascular amyloidosis. The association seems to be there.

Dr. SCADDING: But amyloid may involve other components of the wall of the gut than the vessels, may it not ?

Professor HARRISON: Oh yes, but so often we find only this.

Dr. SCADDING: So probably the diarrhoea was due to the amyloidosis.

THE MENINGITIC EPISODES

Dr. C. PALLIS: The two episodes of lymphocytic meningitis—in November, 1946, and January, 1948—are interesting in this context of widely disseminated tuberculosis. They both subsided without specific treatment. Could they have been tuberculous in origin ? In the ordinary case of tuberculous meningitis there is a massive haematogenous infection of the meninges which in the absence of therapy is rapidly fatal. But occasionally the pattern is different. A small, silent, chronic, local focus—the so-called Rich focus—itself metastatic, flares up, shedding perhaps a few tubercle bacilli, and giving rise to a meningeal reaction. This has been called "serous tuberculous meningitis." The C.S.F. in such cases may show little more than a mild pleocytosis. Such episodes may apparently subside without specific treatment and leave hardly any sequelae. The absence of any meningeal reaction at necropsy in this case does not, I think, exclude this rare variant of tuberculous meningitis. Tuberculosis may be a commoner cause of recurrent lymphocytic meningitis than we suspect.

Dr. SCADDING: Yes, a group of these cases was written up by Edith Lincoln, from New York, in 1947.*

AORTIC VALVE LESIONS

Dr. J. P. SHILLINGFORD: Did the changes in the aortic valve found at necropsy produce any physical signs in life ?

Dr. SCADDING: None at all. Perhaps Professor Harrison would tell us if there is any possibility that these changes could have been due to tuberculous involvement of the myocardium with healing—or were they actually in the valve itself ? It looked to me as if they were in the myocardium at the base of the valve.

Professor HARRISON: There was a small focus of calcification at the base of the left coronary cusp of the aortic valve and a small scar in the epicardium a few millimetres below it.

Dr. SCADDING: It is possible that that lower one might in fact be a scar from an old tubercle ?

Professor HARRISON: My guess is that it is probably a bit of old, organized, thrombotic vegetation.

Professor RUSSELL FRASER: One further point, I don't suppose Dr. Scadding or anybody else can suggest why this patient's tuberculosis was so chronic, or how we could anticipate in another patient such a chronic story. No doubt the availability of antibiotics to-day would make a difference to the degree, but, as you say, this case was unusually chronic for disseminated tuberculosis, wasn't it ?

Dr. SCADDING: Well, my own view is that these variants are more often due to differences in the reaction of the patients than in the virulence of the bacilli. No formal examinations of virulence of this organism were done and we did not find out whether it was human or bovine in type. But it killed a guinea-pig in the usual way and so probably was of quite ordinary virulence.

Professor RUSSELL FRASER: So, if the antibiotics had been available early, it is likely he would have responded very well.

Dr. SCADDING: It was the very slow evolution of the disease to begin with that was so remarkable ; of course, antibacterial drugs just weren't available until he had been ill for two years.

We are grateful to Dr. J. P. Shillingford and Dr. B. E. Heard for assistance in preparing this report and to Mr. W. H. Brackenbury for the photographs.

*Amer. Rev. Tuberc., 1947, 56, 95.

Drug Treatment of Disease

CORONARY ARTERY DISEASE: PART I

BY

M. F. OLIVER, M.D., F.R.C.P.Ed.

Department of Cardiology, Royal Infirmary, Edinburgh

ANGINA PECTORIS

The most important aspect of the treatment of angina is adjustment of the patient's way of living in order to reduce the frequency and severity of attacks. Treatment by drugs is only of secondary importance. More can be achieved by thoughtful rearrangement of the patient's daily routine and activities than by the administration of drugs. The family doctor with his knowledge of the patient's responsibilities is often best able to offer this advice. Reduction of the patient's physical activity will be necessary. Frequently this can be attained by advising small changes such as giving up the use of a bicycle, never hurrying, avoiding hills, and moving the patient's bedroom to the ground floor. Sometimes a change of occupation may be necessary, or retirement may even have to be recommended. On the other hand, unduly severe and artificial restrictions are not advisable, and patients should be encouraged to find out the limits of their exercise tolerance and then to keep within these limits. Every patient requires individual assessment and advice.

Regular periods of rest are essential to the patient with angina. A good night's rest of nine or ten hours, with at least eight hours' sleep, should be obtained, and, if necessary, a hypnotic can be prescribed for this purpose. A complete day in bed at the week-end is often helpful. Patients must endeavour to make it an invariable rule to rest for 20 or 30 minutes after every meal, and heavy meals should always be avoided. For the anxious, restless, worried, and over-active patient, phenobarbitone ½ gr. (30 mg.) can be very valuable twice or three times daily.

Many patients with angina are too heavy. Reduction of obesity, therefore, is important. With the patient's co-operation it can be achieved by a low-calorie diet, and this often leads to improvement of exercise tolerance; dextroamphetamine sulphate and thyroxine are unnecessary and undesirable for weight reduction, since they can produce tachycardia and increase the work of the heart. Smoking should be discontinued. In a few patients angina may have been precipitated or aggravated by anaemia, and will disappear or decrease once the anaemia is corrected.

In a minority, myxoedema can contribute to the development of angina. The administration of thyroid ½ gr. (30 mg.) once or twice daily, or L-thyroxine sodium 0.05 mg. daily, may reduce the incidence of pain, probably by increasing the cardiac output and coronary blood flow. Patients with myxoedema are difficult to manage, since too much thyroid can increase the myocardial demands for oxygen more than the coronary blood flow, with resulting ischaemia of the myocardium and aggravation of angina. Often there is an optimum level of thyroid above or below which angina may occur.

When during a period of a week or two patients develop increasingly frequent episodes of angina, at first on effort and later at rest, a myocardial infarct may be impending. Such patients should be regarded as needing emergency treatment, and, despite their protests of indispensability, admitted to hospital or a nursing-home, where they must be kept strictly in bed. Anticoagulants often appear to have a protective action in these cases (Nichol *et al.*, 1954), and they should be administered for at least three weeks after the episodes of spontaneous pain have ceased. Anticoagulant therapy will be considered in detail in a subsequent article on the drug treatment of myocardial infarction.

It has been emphasized that the drug treatment of angina is of less importance than the general management of the patient. Nevertheless, drugs which relieve anginal attacks should be prescribed to allow of a reasonable amount of activity which otherwise could not be accomplished. Moreover, many patients feel reassured by the administration of a pill, and accordingly their angina often improves. There are many drugs available for the treatment of angina but only a few are of proved therapeutic value.

Nitrites and Nitrates

Short-acting Preparations

Glyceryl Trinitrate.—This is the most widely used and generally beneficial of this group of drugs. In the majority of patients the sublingual administration of 1/130 gr. (0.5 mg.) will relieve an acute episode of angina within two or three minutes or prevent its development when taken in anticipation of an acute attack. Occasionally as much as 1/65 gr. (1 mg.) is necessary to relieve a single episode of pain. Glyceryl trinitrate is also available in the strengths of 1/100 gr. (0.65 mg.), 1/120 gr. (0.54 mg.), and 1/200 gr. (0.32 mg.), and unless otherwise specified it is dispensed in a chocolate base. If chocolate is disliked, glyceryl trinitrate can be obtained in any of these strengths in a base of lactose and glycerine as a white tablet. As its action is short, lasting no longer than 30 to 45 minutes, the dose can be repeated many times each day according to the patient's requirements. Some patients will consume 200 tablets in a week, while others may not require more than 1 or 2. Some, by modifying their way of life, need none at all. The administration of glyceryl trinitrate is commonly associated with peripheral vasodilatation and often with a headache and pounding in the head. Patients with severe angina seldom complain of these side-effects, but if they are troublesome a dose of 1/200 gr. (0.32 mg.) may still relieve angina yet be associated with only minimal side-effects. Patients should always carry an adequate supply of glyceryl trinitrate. The tablets lose potency during the course of a year, and should be kept in sealed bottles, away from the light and in a cool place.

Amyl Nitrite.—This is an effective short-acting volatile nitrite. It is not advocated as a practical treatment of angina, since it is unnecessarily strong and is administered by inhalation; the noise of breaking the glass container, the pungent smell, and the violent facial flush are embarrassing in public. It acts in 10 to 15 seconds but lasts only for 2 or 3 minutes. It has been superseded by glyceryl trinitrate.

Long-acting Preparations

The long-acting drugs in this group are usually disappointing in reducing the incidence or severity of angina but are worthy of trial. There are several in current use, but only two can be recommended.

Pentaerythritol Tetranitrate.—This preparation is of value only in a small percentage of patients, probably less than 20%, but should be given a trial. It is marketed as " mycardol " 30-mg. tablets, and as " peritrate " 10-mg. tablets. It is equally effective sublingually or orally. Oral doses of 30 mg. four times daily an hour before meals are valuable for the patient who experiences pain after a heavy meal, but larger doses may cause dyspepsia. Its action begins after 30 minutes and lasts about 4 hours.

Erythrol (Erythrityl) Tetranitrate.—This preparation is more or less comparable in action to pentaerythritol tetranitrate when given orally in doses of 15 mg. three or four times daily, and is effective in a minority of patients. If before each meal a tablet is allowed to dissolve slowly in the mouth, a greater proportion of patients obtain relief from this preparation than when it is swallowed (Riseman *et al.*, 1958). Its sublingual administration is accompanied by mild peripheral vasodilatation. Its action of 6 hours is valuable, but its continued use sometimes causes a headache.

Other Nitrites and Nitrates.—Sodium nitrite, mannitol pentanitrate, mannitol hexanitrate, and triethanolamine trinitrate biphosphate have little effect and are not recommended in the treatment of angina.

Iproniazid

This is a derivative of isoniazid and is a powerful inhibitor of amine oxidase. Its action in suppressing angina is not yet understood. It probably reduces the appreciation of pain by the cortex (it also relieves the pain of rheumatoid arthritis and carcinomatosis), and it produces a mild euphoria. It potentiates the action of noradrenaline and may, therefore, stimulate coronary vasodilatation. At a dose of 50 mg. three times daily, iproniazid (" marsilid ") produces relief from angina in a majority of patients (Cesarman, 1958; Towers and Wood, 1958), and would therefore seem to be a useful drug. Unfortunately it is associated with many serious side-effects, such as jaundice and liver damage (which may be fatal) and stimulation of the autonomic system. The frequency of these toxic effects greatly limits the therapeutic value of the drug. It may, however, have a part to play in severe and intractable angina in helping the patient over an ischaemic episode; in these circumstances iproniazid therapy should be covered by concurrent tests of liver function.

Antithyroid Agents

Atherosclerotic coronary arteries are often unable to supply sufficient blood for the normal myocardial demands for oxygen, and myocardial ischaemia may result. If the myocardial requirements of oxygen could be restricted, then the reduced blood supply might be adequate. Thyroidectomy, thiouracil (Raab, 1945), and radioactive iodine (Blumgart *et al.*, 1956) have been used to reduce myocardial metabolism, and in a majority of patients reduction of the incidence and severity of angina has followed. Patients who may be expected to gain the greatest benefit from artificial myxoedema are those in whom intractable angina has been present for a year or longer. It is not advised for patients who can be kept moderately active and comfortable by other means. Naturally, patients with angina are often intolerant of the accompanying mental retardation and distressing features of myxoedema, and this form of therapy should be kept as a late resort.

Administration of antithyroid drugs to reduce myocardial metabolism allows easy control of the degree of induced myxoedema, and is less irrevocable than thyroidectomy or radioactive iodine. However, these derivatives do not induce hypothyroidism in every euthyroid patient, and when effective they must be continued for the rest of the patient's life. At any time during such treatment there is danger of agranulocytosis and other reactions to the drug. Carbimazole 20 mg. three times daily, prophylthiouracil 600 mg. daily, or methylthiouracil 600 mg. daily can be given to induce artificial myxoedema. If it is decided that the patient may benefit from artificial myxoedema, radioactive iodine is probably the method of choice. If the initial dose of radioactive iodine is insufficient, additional doses may be given, and, if the patient cannot tolerate the hypothyroid state, it can be alleviated by the administration of thyroid. It is unwise to give radioactive iodine to patients in the terminal stages of the disease, since between five and six months intervene before the maximum benefit can be expected.

Miscellaneous Drugs

There is no satisfactory evidence that khellin, xanthine derivatives, testosterone, or alpha-tocopherol (vitamin E) have any practical therapeutic value in the treatment of angina.

CORONARY ATHEROSCLEROSIS

The dietetic and drug treatment of coronary atherosclerosis is still in the experimental stage and is based on an assumption which is at present unproved. It is that reduction of a high blood level of cholesterol might be associated with inhibition or even regression of atherosclerotic lesions in the coronary arteries. This assumption is based on experimental and epidemiological evidence which suggests that there is a positive and direct relation between the height of the blood cholesterol and the extent of atherosclerotic lesions. The aetiological significance of this relationship and the nature of hypercholesterolaemia are under constant investigation at present, and this is not the place to consider the arguments.

At present it should be emphasized that neither inhibition nor regression of atherosclerotic lesions has yet been demonstrated in man on any regime designed to lower hypercholesterolaemia, but obviously it is difficult to obtain such evidence. Even if atherosclerosis can be retarded, this does not necessarily indicate that reduction of hypercholesterolaemia will improve the prognosis in patients who have already developed clinical features of coronary atherosclerosis. Thus, there is at present no justification for the introduction of any drug or dietetic regime as a routine for patients with ischaemic heart disease.

Reduction of the level of blood cholesterol should be confined to patients who are known to have hypercholesterolaemia, particularly young patients with a strong family history of vascular disease. The principle of the dietetic regimes at present recommended is the reduction of animal fats (saturated fatty acids) with the substitution of vegetable fats (unsaturated fatty

acids) (*British Medical Journal*, 1958). Various drugs have been advocated in order to lower a raised level of serum cholesterol or to reduce the absorption of cholesterol, but there is no therapeutically acceptable drug yet available nor is there any general agreement on the advisability of these procedures.

REFERENCES

Blumgart, H. L., Freedberg, A. S., and Kurland, G. S. (1956). *J. chron. Dis.*, **4**, 381.
Brit. med. J., 1958, **2**, 148.
Cesarman, T. (1958). *J. clin. exp. Psychopath.*, suppl. 1, **19**, 169.
Nichol, E. S., Phillips, W. C., and Jenkins, V. E. (1954). *Med. Clin. N. Amer.*, **38**, 399.
Raab, W. (1945). *J. Amer. med. Ass.*, **128**, 249.
Riseman, J. E. F., Altman, G. E., and Koretsky, S. (1958). *Circulation*, **17**, 22.
Towers, M. K., and Wood, P. (1958). *Brit. med. J.*, **2**, 1067.

PSYCHOSOMATIC DISORDERS IN CHILDREN*

BY

LINDSEY W. BATTEN, M.B., M.R.C.P.
General Practitioner, Hampstead, London

Let me suggest that to speak of psychosomatic disorders, if it implies that certain nameable clinical entities can be so classified, is inaccurate and dangerous—dangerous to clear thought and harmful to our patients. I do not, of course, mean that Psyche and soma are never collaborators or partners in the production of either ill-health or good health. Of course they are. It can even be argued that *every* state of health is due to such collaboration. This is, I suppose, the central tenet of Christian Science, and, though most of us cannot accept it in full, we have, I take it, been driven by irrefutable facts a long way from the materialist front-line of half a century ago.

Allergy and Psychosomatosis

But, while fully admitting that, in my own phrase, Psyche has a finger, and sometimes a fist, in every clinical pie, I still wish to press the point that it is entirely fallacious to make a list of disorders or diseases, whether in children or adults, and term them "psychosomatic." Asthma, urticaria, eczema, rheumatoid arthritis, toxic goitre, ulcerative colitis, duodenal ulcer, and many more disorders or physiological perversities should no more be called psychosomatic than allergic. Their highest common factor is, surely, inherited disposition. They could, not unreasonably, be termed "constitutional," but, like all human affairs, they are due not to one but to a multiplicity of interacting causes.

"In the world of concrete fact," wrote Arthur Balfour (1925), "nothing occurs through the action of a single cause, nor yet through the simple co-operation of many causes, each adding its own unqualified contribution to the total effect, as we picture horse helping horse to draw a loaded dray. Our world is a much more complicated affair."

"Psychosomatosis in childhood" or "children in psychosomatic disorder" should be my title, and I beg you to believe this is not a mere verbal quibble. Let me illustrate.

*Read to the Sections of Child Health and Dermatology at the Annual Meeting of the British Medical Association, Birmingham, 1958.

Susan T., said to have begun to wheeze a little at 5 months, had fairly severe asthma at the age of 10 years in 1938. Asthma was at that time widely regarded as an "allergic disorder," so, though both her mother and I were decently sceptical, to the allergist of the day we had to go. With a mere side-glance at her clinical history, he plunged at once into skin tests, pronounced her sensitive to tomatoes, feathers, horse-hair, pollen, and other things, and advised avoidance of many foods, special pillows and mattress, and a desensitizing course of injections. Her mother and I, in consultation, discovered the flattest contradictions between the skin tests and clinical experience, changed her pillow but forbore to desensitize, and suffered her to continue to eat tomatoes and ride and groom horses, which she did with perfect impunity. We both thought her trouble, at bottom constitutional, was provoked by emotional tensions which we could see and name but not remove.

I shall come back to her case, but my present point is simply that the acceptance of asthma as an allergic disorder threatened to land this child in tiresome deprivations and painful treatment, unsoundly based, likely to fail, and very expensive. Her subsequent history, which I followed for many years, was good; would it have been better if, asthma being psychosomatic, search had been made for forgotten emotional trauma or buried complex instead of for an allergen? I take leave to doubt. Allergy exists, psychosomatosis exists; but let us beware of applying the corresponding adjective to clinical pictures.

"A rash on the hands," it has been well said by Bowers (1958), "might look the same whether caused by 'dettol,' diesel oil, 'distaquaine,' or divorce"; and "on the face almost identical appearances may be given by sensitivity to cosmetics, chrome salts, or just conscience"; and, again, "a nurse may not show her sensitivity to streptomycin until she has some emotional upset."

If pressed I suppose I must concede that facial tics, habit spasms, and the like are, at least at onset, always psychogenic; here is perhaps a psychosomatic disorder diagnosable at sight. But is not soma here a mere indicator, related to Psyche as the railway signal is to the signalman? Psychosomatosis surely demands a more equal and intimate partnership. I think my thesis stands.

How, then, can we know psychosomatic disorder when we meet it? Not, I think, from any static picture, presented at a given moment, but only from the course of events, as learnt by history and observation. The blindness of three blind mice may be psychosomatic, and negative ophthalmoscopy may suggest that it is, but the only sure means to diagnosis in these cases is to see how they run.

Thirty years ago, at the Shadwell Children's Hospital, I saw a child whose constant involuntary movements seemed to me then—and I think would still seem—indistinguishable from true rheumatic chorea. Only when they ceased on admission to hospital but recurred on discharge, and this sequence was several times repeated, was I convinced that the disorder was psychogenic, and the lady almoner discovered for me ample reasons in the child's home. Later I took her into my own house to work in the kitchen and pantry. She proved temperamental, but, sure enough, she never dropped a cup. I know her still, courageously holding down a responsible job despite extreme myopia and retinal detachment.

Only the *course* reveals the psychosomatosis and the diagnosis can be made only by deduction. One more

example will show the elaborate interaction of causes and effects.

Sylvia P.'s father had asthma mildly as a boy and once at 25. I saw him in urticaria—origin uncertain—at 36. Sylvia, a wished-for only child, while thriving at the breast, developed infantile eczema. It became general and severe, yielding only slowly to treatment, which involved restraint of movement. Asthma began as the eczema waned, and a remarkably long-suffering and happy-seeming babe became a lively but very demanding "choosy" and mother-fixed little girl with a long list of "won'ts." One morning she watched her mother being treated in a dentist's chair—no doubt because separation was impossible—and reacted promptly with urticaria, weeping from her eczema, rhinorrhoea, and asthma—"tutti" as a composer might say.

Here, of course, is acute psychosomatosis *in excelsis*, yet constitution had precedence, and the story seems to be one of a disorder arising almost purely from inheritance, with no appreciable determining cause. (It is noteworthy that the babe had an excellent relation to Melanie Klein's (1957) "primal good object"—the mother's breast). Emotional imbalance and disturbance of the mother–child relationship grew directly out of the eczema, and its treatment and was then, it would seem, "fed back" into the machine to convert a constitutional and perhaps in part allergic set of disorders into a demonstrable psychosomatosis.

The Doctor's Job

But perhaps I labour my point. My job, as family doctor, is to recognize disorder of this kind when I meet it and, if possible, correct or subdue it. Having made his diagnosis by deduction from clinical aspect, circumstances, and course, what should the doctor do? First, I believe, ponder it in his heart and be slow to declare it. The psychosomatic concept is not easily conveyed to a mother unless she has already grasped and accepted it, still less to a father. "Nerves" is a most unhappy synonym, and any word beginning with "psych" may carry surprising and unfortunate overtones. Moreover, the sorrows of Psyche are due, all too often, to circumstances quite beyond our power to alter or control.

The father of Susan T., with the non-allergic asthma, was a senior officer in the Army, stationed in Palestine, where her mother had often to be with him. At these times Susan lived in London with a great-aunt 66 years older than herself; when her mother returned she rejoined her in Essex. Neither her mother nor her doctor supposed that this schizoecoid life—if I may coin a word—was good for the child; but what was to be done? Recognize, compensate, where possible, and wait for better times was all that seemed possible to us.

The father of my patient with pseudochorea was a domestic tyrant, doubling the parts of self-righteous bullying parent and openly unfaithful husband. The social services of to-day might possibly have helped more directly than could those of the 1920's, but, then or now, it would be easy to make things worse.

But of course it is not always so. The cause of jealousy, envy, insecurity, and frustration may be obvious to a doctor, though hidden from even a well-intentioned parent, and may be corrigible. On the whole children's emotional problems follow familiar patterns which I need not detail here. Mismanagement at home or at school is much commoner than original sin, but both may exist. The child is not, in my experience, invariably right. There is a Peter Pan in every one of us to be cajoled into growing up.

There is a place, indeed, for the psychiatrist, for play-study and play-therapy, and for all the ingenious devices for working through and expiating and getting things off the chest; but before they call him in I am sure that doctor and mother, in loose or close alliance, should try their hands, remembering that, by and large, time is on their side. "Growing out of" is highly unscientific, but children in psychosomatic disorder often do it, provided they are not fixed in it by over-attention.

Economy and proportion should be the guiding principles of treatment. Fair shares to Psyche and soma, and to each the minimal effective dose. A surfeit of sops to soma—sprays, rays, drops, tablets, elixirs, diets, restraints, unguents, hygienic underware, synthetic pillows, and three-monthly check-ups—will reduce poor Psyche to a doped drug-addict. Throw them all away and give her a cold bath and she may come out new and shining and take command. But there is an opposite error. With our eyes riveted on evasive Psyche we may neglect the crying need of soma for a sedative, an antihistamine, a zinc cream, or a hydrocortisone lotion.

Lucasta, aged 5, was the only child of a late second marriage; her father had vasomotor rhinitis; her mother tried in vain to feed her at the breast. She had suffered from separations from her parents, severe whooping-cough, and, for a time, a repressive nannie. Her Besnier's prurigo began in babyhood, her asthma followed the whooping-cough at 2: she has periodic vomiting; a course of desensitizing injections was suggested for her not long since. She is doing pretty well on breathing exercises (learnt with mother at a good physiotherapy department), day-school, Lassar's paste, mother at home, and phenobarbitone. No restraints and no other medicaments, but the sedative is asked for again when the prescription runs out. A liking for her doctor may have helped too, which brings me to the doctor–child relationship.

I suggest that it is better to be, if we can, from the first, the medical friend and adviser rather than the good wizard, and that this is best done by getting on quietly with the job, explaining as we go. "I don't like doctors who spend so much time making me like them," said a wise child.

I have said nothing of hypnotism, which I am sure is, for some, the method of choice for treating children in psychosomatic disorder. I have no relevant experience, but, from what I read and hear, I gather that while it may abolish symptoms resistant to other therapies it does at best no more; teaching the patient nothing, nor in the least enabling him to tap for himself the vast reserves of autotherapeutic power we all, it seems, possess. I cannot but think that when it fails the confidence of both parent and child must be badly shaken and that when it succeeds the medical friend and counsellor must at least strongly tend to change into the magician.

The doctor's duty to the child in psychosomatic disorder is, as I see it, to instil into Psyche, probably by indirect methods, confidence, courage, clear thinking, and integrity, at the same time treating soma *secundum artem*.

References

Balfour, A. (1925). In *Science, Religion and Reality*, edited by J. Needham, p. 1. Sheldon Press, London.
Bowers, R. E. (1958). *Lancet*, 1, 43.
Klein, M. (1957). *Envy and Gratitude*. Tavistock Publications, London.

DARWINISM AND THE STUDY OF SOCIETY

CENTENNIAL CONFERENCE AT EDINBURGH

[FROM A SPECIAL CORRESPONDENT]

To many of his contemporaries Darwin's work appeared to open up new possibilities for the scientific study of social life and to dissolve the distinction between the natural and the social sciences. Late nineteenth-century writings on society were very largely Darwinian in inspiration; they carried this emphasis to extremes and provoked a powerful reaction. The centenary of *The Origin of Species* seemed therefore a suitable occasion for attempting a reassessment of the relevance of biological principles to social studies, and a centennial conference was held from April 8 to 10 at Edinburgh University, where Darwin was for eighteen months a medical student.

The Human Ecological System

None of the speakers was prepared to accept an absolute separation between the biological and social sciences, but the existence of opposed views on the nature of the relations between them was early evinced in a dramatic series of exchanges between Professor LANCELOT HOGBEN, F.R.S. (Department of Medical Statistics, Birmingham), and Dr. W. STARK (Reader in the History of Economic Thought, Manchester).

Seeking to show why *The Origin of Species* could not have appeared very much earlier than it did, Professor HOGBEN pointed out that it was only in the previous 30 years that improvements in navigation had forced the problems of geographical distribution upon the naturalists; that improvements in surveying had equipped the collector of fossils with contour maps and led to the discovery of geological succession; that optical technology had borne fruit in cardinal improvements to both the microscope and the telescope. At the conclusion of a pungent address, ranging from such matters over questions of palaeontology, physical anthropology, and genetics, he maintained that three factors distinguished man from other animal species: he was uniquely educable, a tool-making organism, and capable of informative communication through speech. He transmitted to the next generation not only his genes but his experience, and thus human society constituted a unique ecological system. Minor variations of the sequence of otherwise similar stimuli might lead to widely divergent responses, and genetic variability was never manifestly the pace-maker in social changes.

Professor Hogben considered that problems of social change could be approached by the study of domestication and commensalism in the human ecological system, examining a sequence such as: given grain storage, then mice or rats, then the cat. How, too, did the existence of a domesticable species attract the attention of man? Was it a coincidence that, before colonization, the American Indians had not perfected the wheel when they lacked horses? There was scope in such questions for fruitful collaboration between archaeologists, cultural anthropologists, zoologists, and botanists.

Dr. STARK reviewed the work of nineteenth-century Continental writers on social selection, in particular Ammon, Lapouge, and Gumplowicz. Ammon, for example, believed that the successful and the unsuccessful in social life represented different streams of heredity. If natural processes made the wheat rise to the top and the chaff fall to the ground, then any step towards equality must necessarily be unnatural and consequently dysgenic. To keep alive those who were inherently dysgenic and whom Nature had marked down for destruction was a stupidity which would drag its own condign punishment after it. Dr. Stark showed how these theories, in so far as they were not self-contradictory, led to the racialist philosophy of Nazi Germany. Darwin, he said, would have been horrified had he foreseen the uses to which his doctrines were to be put after his death. The extension of natural selection from the animal to the human sphere was not legitimate. Laws of nature served to delimit an area of freedom, which we knew as culture, within which selection occurred on the basis of values.

This distinction drew the fire of several speakers. The chairman, Professor JAMES DREVER (Department of Psychology, Edinburgh), pleaded for a biology of symbolizing organisms. Professor HOGBEN could not see how Nature and human nature were to be separated. He protested that according to Dr. Stark the social Darwinists had got their biology right but had not read enough Kant to know when it was applicable; he held that they had got their biology wrong.

Evolution and History

Two speakers discussed Darwin's work from a historical perspective, but historical consideration also entered the discussion by way of analogies between the evolutionary process and the course of human history. Mr. G. A. SHEPPERSON (Department of History, Edinburgh) examined the intellectual background of Darwin's student years at Edinburgh, and concluded that he had learned a great deal more while there than the rather ungenerous remarks in his autobiography would suggest.

Professor BASIL WILLEY (Department of English Literature, Cambridge) delivered an introductory address in which he sketched Darwin's place in the history of thought, dealing chiefly with the development of the hypothesis of evolution and the impact of Darwin's writings upon religious beliefs. Darwin would turn in his grave, said Professor Willey, if he could know that anyone would salute him as an unwitting champion of Christendom, but Darwin had positively helped to restore buoyancy to religion by forcing it to abandon some of its most untenable defences.

Professor C. H. WADDINGTON, F.R.S. (Institute of Animal Genetics, Edinburgh), gave the conference an account of current views on the human evolutionary system. It comprised four major sub-systems: the exploitive, the epigenetic, the genetic, and that of natural selection. An animal chose an environment, modified it, and was there subject to environmental stresses which revealed its potentialities: these factors set the stage for the operation of hereditary variation. In subhuman species transmission to the succeeding generation occurred at the point of fertilization only. In man there was a second evolutionary system superimposed upon the biological one and functioning by means of the continuous transmission of information. Most human evolutionary changes of real importance had been produced by the action of this second system.

Both biology and sociology were so undeveloped that they were still trying to make inventories of all the processes that ought to be taken into account. It was worth while investigating the parallels and contrasts between the two systems, for biological analogies might raise questions of significance for sociologists. One parallel lay in the linkage of characters. In genetics linkage might be purely contingent—as when two genes lay on the same chromosome—or functional, as when two characters co-operated to produce a co-ordinated organism. When was the grouping of social characters contingent or functionally interdependent? The combination of industrialism with the wearing of trousers (most marked in the under-developed territories) appeared to be contingent, but its association with a strict sexual morality did not.

The two major items of the subhuman evolutionary system were mutation and selection: what corresponded to them in the human evolutionary system? Was there

any chance mutation in the establishment of religions, or did they arise from interaction between peoples and their environment? What decided, furthermore, whether new variations in the social world would persist? Why, for example, had Mendel's work been neglected for 50 years and had Lamarck's name become almost a term of abuse? There appeared to be some factor at work in society which corresponded to natural selection.

In a commentary upon this address Mr. J. MAYNARD SMITH (Department of Zoology, University College, London) concentrated upon parallels between history and biological evolution. In both we were faced with change, not with repetition, and had to deal with a system of interdependent relations about which no long-term predictions could be made. However, that was almost all they had in common. He doubted if any helpful theory of history could be derived by starting from evolutionary theory and attempting to find historical analogues for the various entities and processes involved. Though incomparably more was known about the course of history than of evolution, historians had developed no general theory. Nevertheless he thought that to give up the search for one would be to throw in the sponge too early in the fight. The most successful attempt hitherto had been the theory advanced by Marx; its weakness lay not in any fundamental error in its author's approach but in the failure of his followers to treat his ideas critically or to modify them in the light of advances in other fields. In biology the dialectic approach often made simple problems complicated and substituted vagueness for precision; occasionally it had disastrous consequences.

Social Evolution

Professor MORRIS GINSBERG (Emeritus Professor of Sociology, London School of Economics) considered that while no laws of social development had been discovered —and certainly none of progress—long-range trends could be discerned which showed that progress had occurred along certain lines. In human evolution progress consisted in the growth of rationality—that is, the systematic organization of thought and experience. Thus the secularization of law and politics had contributed to the growth of civilization by removing from the category of criminal and punishable actions matters of belief, such as atheism, heresy, and schism, or the non-performance of religious rites, as well as, for example, certain sexual offences. Whether the advance in the control of Nature made for progress depended not only on the growth of knowledge and of moral insight but on the extent to which these were embodied in social institutions and through them shaped behaviour and moulded character.

Professor BENJAMIN FARRINGTON (Emeritus Professor of Classics, Wales) criticized "technozoism" as a modern scientific illusion. Underlying the arguments of certain physiologists and cyberneticists was the implicit assumption that the brain was an organism biologically evolved for turning sensations into concepts. In fact, the advance from the biological to the social level was one to phenomena that could not be explained in exclusively biological terms. In human history, as Gordon Childe had written, "random mutations are replaced by discoveries and inventions," and these "are transmitted not by copulation but by education." Social institutions were not part of Nature. There was, for example, no such thing as the "natural family"; the family was an institution inexplicable except by the intervention of a collective human force acting through constituted authority. Neither the wearing of clothes nor going naked, neither eating nor defaecation as performed by man, were acts of Nature. They were regulated human methods of dealing with Nature carried out in accordance with conventions and rules.

Communication in Animal and Human Societies

The third day of the conference opened with a session devoted to the study of communication. Mr. S. A. BARNETT (Department of Zoology, Glasgow) argued that zoology could make three main contributions to the study of human communication. Firstly, it could throw light on behaviour in infancy. Secondly, as Darwin implied, it could stimulate fruitful comparisons in the field of motivation or emotion. Thirdly, it could illuminate the dual nature of human communication—both exhortatory and descriptive. Sucking, crying, smiling, and clinging were all means used by infants to convey information to a parent.

Recent research indicated that "social smiling" on the part of babies awakened tenderness in previously unloving mothers and might therefore, he said, have survival value (though this interpretation was later criticized by Dr. BRONOWSKI). Contact with other human beings was of profound importance in infancy—as indeed at other ages. Laboratory rats, if regularly stroked by the experimenter each day early in life, were later better at learning to run mazes, and, what was more important, they grew better, resisted stress better, and were less emotional.

Mr. TOM BURNS (Social Sciences Research Centre, Edinburgh) held that the link between animal and human communication was its fundamentally normative character. The experimenter had always to be sure that the specimen he was using was a "good" one, that it was representative of its kind. In social life, action was only possible when a degree of consensus existed between participants as to what the norms of conduct were. The characteristic feature of animal behaviour and communication systems was that there tended to be a one-to-one ratio between ends and means. There were no alternative norms for action in an emergency, or very few, except perhaps where deviants or abnormal specimens were involved. Change, if it occurred at all, occurred through the lives and deaths of generations. In human affairs the process of behavioural change could, perhaps rather fancifully, be seen as projected on to the mediate and artificial population of social norms, with occasional lethal consequences for individuals and groups who got caught up in a one-to-one ratio between the ends they pursued and the social procedures available to them.

Darwinism in Retrospect

Dr. J. BRONOWSKI (Coal Research Establishment, Cheltenham) told the final session of the conference that many people who voiced opinions on social science continued, under the banner of Darwinism, to interpret eighteenth-century doctrines and apply them to race, class, or intelligence groups, without regard to factual evidence. A glaring example of this was to be found in the tortuous arguments of the second survey of the intelligence of Scottish schoolchildren.

The concept of the survival of the fittest, which played so important a part in some of these doctrines, was, he said, a tautology. Taken at its face value it should mean that one species, and one only, should by now predominate. Fitness, however, did not just mean appropriateness. The coelacanth had survived because it had been able to avoid pursuit, not because it was adapted to its environment. As Professor Waddington had made clear, hereditary elements were transmitted in groups and the combination of factors produced something much more complex than a collection of separate factors. It had been suggested that in human society inventions were the closest analogues to genetic change. Dr. Bronowski would like to have heard more detailed suggestions for the study of correlated change. The question of what hung together and what failed to do so was now central to the study both of physics and of biology.

In 1859 an appealing theory had been offered as to the origin and proliferation of life. Its popular success lay in its polarizing the possible answers, its scientific success in provoking biologists to inquire into the origin of hereditary variation. Darwin could not answer this question. He constantly used phrases like "variability seems to us in our ignorance to be spontaneous." The

greatest significance of his work lay in his having posed this question—in having made Mendel necessary. Genetics had located the pool of potential variability and more recent research had established that mutation replenished that pool. The study of society had not yet discovered any pool of simple forms of behaviour out of which changes in society could evolve. The units of variability were still undetected.

It was sometimes held that the weakness of Darwin's system lay in its dependence upon chance mutation, but Dr. Bronowski saw in this its strength. By introducing chance effects into a developed scientific theory, Darwin not only contributed a fundamentally new idea to our view of Nature, but paved the way for fruitful research in the physical sciences. Planck's quantum theory of 1900 was still of contemporary interest though it was nearer in time to 1859 than to our own day. In his substitution of chance for design as a basic explanatory concept Darwin had been more radical than Newton. Though Newton had disturbed traditional beliefs, he had provided a causal account of the Universe with the Almighty standing by to correct the errors of chance arising from the operation of the laws of gravitation. In Darwin's elevation of chance lay the root of the religious reaction against evolutionary theory.

Professor ASA BRIGGS (Department of History, Leeds), appraising the discussions from the standpoint of the humanities, dealt first with the relations between the biological and social sciences in Darwin's day. Like Dr. Bronowski, he was critical of Professor Willey's presentation of Darwin as an unwitting champion of Christianity. It was not true that Darwin was a Victorian country gentleman who thought that the world would not be interested in his private opinions on non-scientific topics. He knew the world would be only too interested and was afraid of splitting his family. The way his autobiography had been expurgated showed that his fears had been justified.

The Origin of Species led people to see society as an organism rather than a mechanism and to look for development rather than balance, but it reached out to a popular audience through the medium of magazines and reviews that were interpretative rather than factual. Social Darwinism had been a popular polemic providing a new language for old cleavages between weak and strong, imperialists and colonials. In this sphere Darwin provided not so much a dynamic as a rationalization. The influence of social Darwinism could be overrated and the forms of its expression had to be related to the environment of its authors; whether true or false, Darwinian analogies could lend themselves to diametrically opposed conclusions in the social and political sphere.

To-day there was a completely new configuration of learning. It was generally agreed that, though human evolution was continuous with animal evolution, the clues to the study of changes in human society were not to be found in genetics. Nor could there be any easy transfer of terms (such as the use of "need" for "desire") about which there would always be controversy. Analogies, too, were dangerous and their main value lay in prompting hypotheses. While he felt sympathetic towards Professor Waddington's suggestions in this regard he doubted if they could prove very helpful. Each scientist had to work from the facts before him and to use the theories that fitted them.

What part could the historian play in this? Professor Briggs considered that the gap between historical problems and controlled experiments was tremendous; nevertheless more could and should be done to organize historical research so that different studies were complementary. In this country the history of society was thought of as a substitute for political history, or was swayed by fashion rather than by discipline. It needed to be linked with sociology because the variety of studies pursued in this field permitted problems to be viewed from many aspects and for different research workers to keep in touch with one another.

The papers presented to the conference are being prepared for publication.

Nova et Vetera

PROGRESS 60 YEARS AGO

Dr. J. W. Bride, F.R.C.O.G., recently found the address we print below among the papers of his father, Dr. John Bride, of Wilmslow. It was Dr. Bride's presidential address at the first meeting of the East Cheshire Medical Society on December 13, 1899.

It will be within the recollection of some of you here to-night, that some five and twenty years ago, a Society was formed in Macclesfield on lines similar to that of the one we are met here this evening to inaugurate. That Society, for reasons which it is not now necessary to particularize, did not enjoy a long existence, and after a few years of not very vigorous life, died of inanition. Let us hope that a better fate awaits the Society whose birth we are here to-night to inaugurate.

Twenty-five years is a long period in the life of an individual, short in that of a community or body corporate; and it occurs to me that a brief glance at the various improvements, alterations, and innovations which have taken place in Medical Science during the above period may not be without interest; and first allusion may be made to the compulsory notification of disease. Twenty-five years ago compulsory notification was practically unknown, the subjects of measles, scarlatina, and smallpox were allowed, during a stage in which they were still infectious, to mix with other members of the family, and in this way disease was soon broadcast. Now, thanks to better legislative regulations, each case is confined as far as possible within its own area.

In connexion with this subject may be mentioned the still more interesting one of the voluntary notification of phthisis. One reads that the health committee of the Norwich City Council has agreed at the suggestion of its medical officer[1] to make a trial of the value of the voluntary notification of phthisis. The experiment is to commence on January 1 next, and is to last for six months. Notification is to be voluntary, but the health committee has to pay a small fee for each notification. It is believed that much valuable information as to the distribution of phthisis may be gained in this way. The medical officer has expressed the hope that there may be sufficient to justify him in advising a continuance of this voluntary notification, possibly until tuberculosis is included by Act of Parliament in the diseases to be notified compulsorily. It is not doubted that valuable results may be obtained by the notification of phthisis. The medical officer of health of Brighton[2] has shown the possibility of notification, and its utility there. Nearer home Dr. Niven[3] has advised the adoption of a similar plan in Manchester; insanitary conditions may thus be brought to the notice of the M.O.H. and the prevalence of the disease diminished by the removal of such insanitary conditions.

The foregoing remarks bring me to the consideration of the open-air or sanatorium treatment of phthisis. Phthisis, we are told, is no longer phthisis, or, as we familiarly call it, consumption. It is a tuberculosis of the lung. The name open-air treatment referred only to one factor; sanatorium treatment was possibly a better term. Tuberculosis of the lung may be arrested by residence in a favourable climate merely, but it was less likely than under the sanatorium method with pure air and a moderate elevation. So long as phthisis was believed to be a catarrhal process, all measures for excluding cold air were adopted, but, now that its nature was recognized, an open-air life was desirable. In these sanatoria great attention is paid to temperature and frequent thermometrical readings are made, the observations being taken in the rectum. When for a week the temperature has been below normal in the morning, and below 100.4° F. in the afternoon, graduated exercise is taken, the most suitable being slow up-hill walking, thus strengthening the

heart and promoting complete expansion of the lungs. Dr. Kingston Fowler,[4] an authority on this subject, thinks the method has come to stay, aiming, as it does, at increasing the resisting power of the body in every way. Even as I write, the importance of this mode of treatment seems to be permeating public bodies, not usually amenable to the spirit of progress, especially in matters medical; I mean the Boards of Guardians, and we are told that three of the large Unions of Liverpool have combined for the purchase of an estate overlooking the river Dee, on which to erect a sanatorium.

The preventive treatment of typhoid has lately received a fresh addition in the introduction of anti-typhoid serum. This method of protective inoculation we owe to Professor Wright,[5] an Army surgeon of Netley, and though its value is not yet definitely settled, it has given sufficiently encouraging results to justify a trial on an extended scale. Large numbers of men ordered to South Africa have been inoculated on embarkation, and on their arrival there. In connexion with this must be noticed Widal's serum test for the diagnosis of typhoid. This, though more applicable to the scientist in his laboratory than to the general practitioner, is still a valuable addition. There are not many of us who in the first days of our typhoid cases have not experienced some doubts and difficulties as to the diagnosis.

Very striking also is the advantage which surgery and medicine have derived from the use of the Roentgen rays. It seems as though military surgery would have to be rewritten, and the wounded will no longer have to look forward with dread to the painful probing after bullets, which used formerly to take place.

Just lately a marked advance has been made in the investigations as to the origin of malarial diseases. Major Ross,[6] of the Liverpool School of Tropical Medicine, has shown that the parasites of malaria pass a stage of their existence in certain species of mosquitoes, by the bites of which they are inoculated into the systems of men. Hence it follows that in order to eliminate malaria from a certain locality it is only necessary to exterminate the various species of insect which cause the infection. In order to do so it seems to be sufficient to empty out or drain away, or treat with certain chemicals, the small collections of water in which the larvae pass their existence.

Only a passing allusion can be made to serum therapy, which, in its various developments of antidiphtheritic serum and antitetanic serum, antiplague serum and antistreptococcic serum, has proved itself eminently valuable. More especially is this so in the case of antidiphtheritic serum, which, as an eminent writer has said, places moral obligation on medical men to use it for diphtheria patients.

Gentlemen, I have touched very briefly and imperfectly some subjects of great interest to us as medical men. I thank you for having listened to me so patiently, and can only hope that I have not wearied you.

It only now remains for me on behalf of the East Cheshire Medical Society to offer you one and all a hearty welcome, and to express a hope that it may be the means of promoting social intercourse, union, and good will amongst its members.

NOTES

[1] Harry Cooper Pattin (1862–1930) was appointed medical officer of health for Norwich in the late 'nineties and retired in 1926.

[2] Sir Arthur Newsholme (1857–1943) was M.O.H. for Brighton from 1888 to 1908, when he was appointed principal medical officer to the Local Government Board.

[3] James Niven (1851–1925) was M.O.H. for Oldham from 1885 to 1894 and for Manchester from 1894 to 1922.

[4] Sir James Kingston Fowler (1852–1934) was physician to the Middlesex Hospital. He became consulting physician to King Edward VII Sanatorium and the Brompton Hospital and published several important works on pulmonary tuberculosis.

[5] Sir Almroth Wright (1861–1947). A preliminary note on his work in connexion with antityphoid inoculation appeared in the *Lancet* in 1896.

[6] Sir Ronald Ross (1857–1932). His proof that the mosquito was responsible for the transmission of malaria had appeared in the *British Medical Journal* two years previously.

To-day's Drugs

With the help of expert contributors we publish below notes on a selection of drugs in current use.

OnychoPhytex (Wynlit Laboratories).—This is borotannic complex 9.92% in alcohol and ethyl acetate, and is available in bottles of 30 ml.

Ringworm of the nails is becoming more common and presents an almost insuperable therapeutic problem. It is claimed that onychophytex penetrates the normal nail and the infected nail, and that, having done so, it exerts a lethal effect on the fungus. There have been reports of clinical trials which have been carried out in several European centres; on the average a cure rate of 65% is claimed provided treatment is thorough and prolonged. This is no doubt a better rate of cure than is obtainable with any other method up to the present: possibly griseofulvin will give results which are as good as or better than these, but it is too early to say yet. A full-scale clinical trial does not appear to have been carried out in the United Kingdom, but, in view of the extremely unsatisfactory results of other methods of treatment, onychophytex seems to be worth a trial.

N.H.S. basic price: 30 ml., 10s. 10d.

Suramin *B.P.*

Antrypol (Imperial Chemical Pharmaceuticals).

This is a complex organic compound of urea. Its principal uses are two in number: as a trypanocide valuable in the early stages of trypanosomiasis, and as one of the substances which may be used in the treatment of onchocerciasis.

Suramin does not pass the blood–brain barrier because its molecule is so large, and it is therefore not of value in cases of trypanosomiasis in which the central nervous system has become involved, but in early cases it is very effective.

In onchocerciasis its action is slow and no immediate relief from pruritus, ocular symptoms, or other manifestations of the disease is to be expected. It appears mainly to affect the adult worms, whereas symptoms are mostly produced by microfilariae. After treatment with suramin, therefore, symptoms diminish in severity only over weeks or months as adults die and cease to produce microfilariae. Consequently, it is probably best to give courses of both suramin and diethylcarbamazine, for the latter rapidly kills microfilariae but has only a slow action upon the adults.

Administration should only be intravenous; if injected intramuscularly, suramin causes necrosis and swelling of tissues, much pain, and in some cases a persistent sinus. When given intravenously 1 g. is dissolved in 10 ml. sterile distilled water. For trypanosomiasis this amount is usually given twice weekly for the first week and thereafter at weekly intervals until 7–10 g. has been administered. For onchocerciasis 1 g. is usually given weekly for 5–8 weeks.

The principal toxic reaction, which unfortunately is easy to overlook, is development of nephritis. This seldom occurs until 2–3 g. have been administered, and it is then marked by the presence of albumin and casts in the urine. In order to avoid doing permanent damage to the kidneys, the urine should be examined for albumin and casts before each injection is given, and if either are present further treatment with suramin should be postponed until the urine has become normal again. Alternatives which may be used during such a period are pentamidine for trypanosomiasis and diethylcarbamazine for onchocerciasis. Occasionally an irritable papular rash may complicate treatment with suramin, and more rarely severe exfoliative dermatitis has been reported.

N.H.S. basic price: 25 ampoules 1 g., 26s. 3d.; powder 5 g., 4s.

Correspondence

Because of heavy pressure on our space, correspondents are asked to keep their letters short.

Human Fascioliasis

SIR,—Coincident with a succession of wet summers there has been a sharp increase in the infestation of farm animals with the liver fluke, *Fasciola hepatica*. Human cases have rarely been reported in this country, but that they may be expected is suggested by the recent occurrence of a small outbreak affecting four people in a Hampshire market town. A few notes may be helpful.

The disease is usually acquired from eating watercress, of which fateful herb all our patients were enthusiastic consumers. The onset is often insidious, with increasing asthenia, inability to work, and loss of weight. There may be generalized abdominal discomfort at first, but in most cases there soon occur severe bouts of pain localized in the liver, which may be enlarged and tender. An irregular pyrexia may be an early feature and can last for months. One patient complained of cough and a sense of constriction in the upper thorax without any abdominal symptoms.

Such histories as these are hardly pathognomonic, but, if the symptoms persist, a blood count is indicated and an eosinophilia of 20–60% provides the first real clue. Unfortunately this useful pointer is not always present. It is important to remember that confirmation may be difficult, as it is said that the ova are seldom found in the faeces until three months after infection.[1] This has also been our experience. Special methods of concentration of the specimen are necessary.[2] A complement fixation test may be helpful.

Professor A. W. Woodruff and the staff of the Hospital for Tropical Diseases very kindly confirmed the diagnosis and instituted treatment with chloroquin in one case.

It is proposed later to publish a full report on these cases together with all due acknowledgments.—I am, etc.,

Royal Victoria Hospital, Boscombe, Bournemouth. R. VAUGHAN FACEY.

REFERENCES

[1] *Lancet*, 1957, **2**, 882.
[2] *J. clin. Path.*, 1956, **9**, 74.

Long-term Anticoagulant Therapy

SIR,—The publication of the M.R.C. Working Party's report on the clinical effects of anticoagulants (*Journal*, March 28, p. 803) and your leader in the same issue (p. 838) have aroused great interest and perhaps some misgiving. Over the controversial question of the treatment of myocardial infarction the doctor, especially the consultant, finds himself in a worse quandary than before. If these findings are followed, men under the age of 55 with severe myocardial infarction must be given the benefit of the doubt in the shape of anticoagulant therapy for six months after the infarct. Our already overcrowded out-patient clinics and pathological services may be able to cope with this group for this period of time, but will it stop there? One feels that it will not. If prolonged anticoagulation is indeed a protection against further infarction, it is hard to believe that the results of future studies will agree with an arbitrary limitation of the period of treatment to six months. One sees the beginning of a snowball, and the widespread establishment of "anticoagulation clinics," some of which already exist. If these are necessary they will of course come, just as did diabetic clinics with the advent of insulin. A few of us, however, although willing to be converted, are still not entirely convinced of the value of anticoagulation therapy. There is, for example, the series of Honey and Truelove,[1] a careful study which failed to support the enthusiasm of others. Without wishing to appear naive, I have long wondered how prolongation of the prothrombin time can be expected to prevent thrombosis. Such an effect by heparin which prolongs the coagulation time of blood and has a somewhat complex effect on fibrinolysis is easier to believe.

My purpose in writing this letter, however, is not to question the conclusions of a well-designed trial sponsored by such high authority, but to contrast the present management of myocardial infarction with the recommendations implicit in your leading article. The management of the patient with presumed myocardial infarction in the first place depends on his family doctor, and individual practice is not uniform. Doctors differ in this connexion as follows: (1) A small number who if satisfied on clinical grounds that an infarction has occurred treat the patient at home without reference to the hospital or consultant services. (2) Those who refer all patients with suspected infarction to hospital for admission. (3) Those who utilize a consultant domiciliary visit to confirm infarction by electrocardiography, the time after infarction at which the consultant is asked to see the patient varying from 24 hours or less to a week or more.

The first group of patients, a small one, is not seen by a consultant and presents no problem from his point of view. The second group is started on anticoagulant therapy after admission and also according to present-day convention presents no problem. The third group is more difficult. Unfortunately the peak periods of myocardial infarction, respiratory infection, and haematemesis coincide, resulting in a sometimes overwhelming pressure on medical beds. I therefore advise home treatment of uncomplicated infarcts, especially if I am not asked to see the patient until a week or more after the infarction, a practice with which most family doctors concur. Often, however, I am asked whether an anticoagulant of the prothrombin-antagonist group should not be given "blind" in moderate dosage. To my mind it is axiomatic that prothrombin-antagonists should never be given without laboratory control, except as a loading dose before admission to hospital. If given "blind" the risk of haemorrhage is far greater than the expected benefits, and when given in this way in small and ineffectual dosage an anticoagulant represents no more than a placebo for the doctor. The emphasis in your leading article on the necessity of laboratory control in anticoagulant therapy is therefore timely in relation to the M.R.C. report.

If anticoagulant therapy does reduce the mortality and morbidity resulting from myocardial infarction, and there is an impressive body of evidence that it does, albeit with some dissenters, it follows that, save in exceptional circumstances, every patient with an infarct should be admitted to hospital. In the presence of a disease of apparently increasing frequency, we are faced with yet another situation where the bed situation is inadequate for the demands made upon it. If long-term anticoagulant therapy is to become an accepted ritual, our out-patient departments and consultant man-hours will be similarly affected. It is therefore to be hoped that some measure of agreement for or against long-term anticoagulant therapy will soon be reached if only

because the present situation in this litigious age may put the physician who does not adopt it in peril.—I am, etc.,

Gloucester. G. R. FEARNLEY.

REFERENCE

1 Honey, G. E., and Truelove, S. C., *Lancet*, 1957, **1**, 1155, 1209.

Cortisone and the Acute Red Eye

SIR,—Since the corticosteroids became generally available many practitioners are prescribing them for the acute red eye indiscriminately. They are often given (either alone or with an antibiotic) without a definite diagnosis being made, and their use in this way may be misleading, wasteful, and sometimes dangerous. As elsewhere in the body, cortisone in the acutely inflamed eye may damp down the signs, whatever the primary cause of the inflammation. In many cases the eye whitens and the symptoms abate. This may happen even if the cause of the inflammation is some simple mechanical irritant—e.g., a foreign body or inturning eyelash which has not been observed.

Acute bacterial infections (conjunctivitis, etc.) may be made worse by the use of cortisone alone; the proper treatment is chemotherapy, and most British ophthalmologists would regard cortisone as an unnecessary adjunct. In iridocyclitis cortisone and its derivatives are the specific therapy, but here again the unwitting correct use of cortisone, perhaps in inadequate dosage and without mydriatics such as atropine, may lead to the pupil margin becoming adherent to the lens. In acute primary glaucoma cortisone is worse than useless; it has no effect on this condition and merely leads to prolonging the patient's agony, until such time as anti-glaucoma therapy is started.

Particular attention should be drawn to the effect of cortisone on corneal ulcers, which are a frequent cause of the acute red eye. While it is true that some types of ulcer—e.g., the marginal ulcer—do well on cortisone, it is equally true that many other types and probably the majority are unaffected or do badly. Ulcers of virus origin, especially the common dendritic ulcer, may be made much worse—some authorities even feel that cortisone may actually light up latent virus infections of this type. In their initial stages these ulcers do best by the time-honoured methods of cauterization. An undiagnosed and cortisone-treated dendritic ulcer is becoming all too frequent a condition in eye out-patient clinics. Spreading ulceration surrounded by soggy epithelium in an eye which is practically white, with perhaps slight photophobia and watering, is the clinical picture. The symptoms, minimal in relation to the signs, are yet sufficiently serious or persistent for the patient or his practitioner to seek further advice.

It would be interesting to hear whether the writer's experience is shared by others. If so, it must be clear that the haphazard prescription of cortisone for the red eye may be increasing ocular morbidity.—I am, etc.,

Moorfields Eye Hospital, London, W.C.1. J. D. ABRAMS.

Sarcoma in the Rat

SIR,—Dr. H. G. Richmond (*Journal*, April 11, p. 947) describes the induction of sarcomas in rats by giving repeated injections of "imferon." His report will naturally raise in the reader's mind the possibility that imferon injections may be dangerous in man. In 1953 we gave up the idea of using powdered polytetra-fluoro-ethylene as a lubricant for knee-joints when we found that in a rat's muscle a single injection of this most inert of substances induced a histological reaction of a neoplastic nature. Since then we have learnt that many irritant and non-irritant substances will induce sarcomas at the site of injection in rat muscles. The non-irritants include not only a wide variety of plastics, some of which are used in man, but also certain vehicles for medicaments that are given by intramuscular injection. These latter have been used very extensively for many years, and, to the best of my knowledge, there has not been a single report of an induced sarcoma. It would appear that this is one of the ways in which we differ from rats.—I am, etc.,

Nether Edge Hospital, Sheffield, 11. H. F. WEST.

Rubella in Pregnancy

SIR,—May I propound some cases, imagined but quite possible, to test the validity of the proposition that "rubella in the early weeks of pregnancy . . . constitutes a risk *one cannot allow to be taken*"?

A woman of 35, ideally married for a year, becomes pregnant. In the sixth week her husband is drowned while saving a life; in the eighth she gets rubella.

A wife of 43 at last achieves a longed-for pregnancy and gets rubella "in the early weeks."

Two married women—twins, if you like—get rubella; one in the third week of pregnancy, one in the tenth.

Are *all* these women to be told out of hand by their family doctors that their pregnancies cannot be allowed to continue?

One more imagined case. A young woman is her husband's right hand and the mother of three children. All is well with the family, but they have no relations "to fall back on." She becomes pregnant again and gets rubella—let us say late in "the early weeks." Most reluctantly she accepts our inflexible advice that the pregnancy "cannot be allowed to continue." It is terminated, but she dies of pulmonary embolism on the fourteenth day.

Surely, Sir, two things are clear. (1) We can no more hide behind a rule in this than in the matter of telling a patient he has cancer. We must decide what we believe to be best, and best rather for the patients we can touch and see than for the embryo or foetus—impalpable, invisible, unknowable. (2) We have no right or duty to do more than put before wife and husband the relevant facts as we know them, and advise what we think to be the lesser evil. If they decide to take the risk, can we possibly have any other duty than to guide the pregnancy, if we can, to a normal issue?—I am, etc.,

London, N.W.3. LINDSEY W. BATTEN.

SIR,—The doctor, faced with the question of advising a woman who has contracted rubella during the early part of pregnancy, is in urgent need of information about the risk such a patient runs of giving birth to a malformed baby. Dr. Julia Bell (*Journal*, March 14, p. 686), while rightly admitting that no definite calculation of the risk involved is yet possible, advises a very drastic course of action, basing her advice on evidence which we believe to be unsound. The unreliability of retrospective surveys in this connexion has been stressed so often that their use could only be countenanced if no surveys of the prospective type were available; but several prospective surveys have been done. In our review of six sources in which the study was definitely prospective, including our own survey,[1] the risk in a total of 92 cases of maternal rubella in early pregnancy varied from 10 to 30% with an average of

18%. Bradford Hill *et al.*[2] record a risk of 50% in the first month, but this fell to 25% in the second and 17% in the third month, with an average for the first 12 weeks of 28%. In the absence of a definite estimate of the risk or of any explanation of the great variations in the estimates that have been recorded, a very dogmatic attitude is surely difficult to justify.—We are, etc.,

Department of Social Medicine, Trinity College, Dublin.

VICTORIA COFFEY.
W. J. E. JESSOP.

REFERENCES

[1] Coffey, Victoria P., and Jessop, W. J. E., *Irish J. med. Sci.*, 1959, 6th series, p. 1.
[2] Hill, A. B., Doll, R., Galloway, T. McL., and Hughes, J. P. W., *Brit. J. prev. soc. Med.*, 1958, **12**, 1.

SIR,—I share Professor H. C. McLaren's "very sincere doubts" (*Journal*, April 4, p. 921) about accepting Dr. Julia Bell's answer to the problem of rubella in pregnancy (*Journal*, March 14, p. 686). He feels that perhaps Dr. Bell will think his approach to terminating pregnancy lacks "fierce logic," but would not the logical thing be to allow the pregnancy to proceed to term (after all the mother is not at risk) and then murder only the affected children? Thus the Herod-like slaughter of the unaffected would be avoided—but this is absurd. Q.E.D.—I am, etc.,

The General Hospital, South Shields.

T. G. ROBINSON.

SIR,—Professor H. C. McLaren has made clear his reluctance to advocate the termination of pregnancy following maternal rubella (*Journal*, April 4, p. 921). May I be allowed to question a few of the points raised in his letter?

Among the factors that he recommends should be taken into consideration in arriving at a decision is the severity of the rubella. From my own experience I can assure him that the degree of congenital malformation is not always related to the severity of the rubella, and that the most severe foetal involvement can follow a very mild and transient maternal infection.

Secondly, Professor McLaren recommends that we should "share our German measles with other families." Second attacks of German measles, though rare, do occur, and I know of four children with severe congenital defects as a result of proved second attacks. Moreover, there is evidence that foetal involvement in second attacks is more severe than in first infections. We cannot therefore rely upon childhood infection to offer protection.

Lastly Professor McLaren tells us that by terminating pregnancy "the chance of removing a perfectly normal child is perhaps as high as 8 or 9 out of 10." That this proportion is a little high is suggested by Jackson and Fisch's prospective,[1] and therefore reliable, estimate of 26.3% of major defects following infection in the first 18 weeks, and the 23.8% of Bradford Hill *et al.*,[2] quite apart from the more disturbing but less reliable figures of Dr. Julia Bell.

The real problem, however, is not one of statistics, but is individual. When a pregnant mother, having had rubella, is aware of the risks and is prepared to face them, then no one would try to persuade her to accept termination. But if she feels unable to face the appalling anxiety of a pregnancy overshadowed by fear of a blind or deaf child, then it requires strong convictions to refuse her request. The mother who has asked for termination and has been refused it has a hard task to avoid some bitterness in accepting the burden of a handicapped child, and I know of two such cases.

Finally, like Professor McLaren, I must admit to some emotional bias. As the father of a boy trebly handicapped following maternal rubella, I would ask only that we do not adopt too rigid an attitude to this problem, that we treat each mother who finds herself in this situation as an individual problem, and that we do not allow statistics to blind us to what we are asking of these patients.—I am, etc.,

Saint Bartholomew's Hospital, Rochester, Kent.

BEVIS H. BROCK.

REFERENCES

[1] Jackson, A. D. M., and Fisch, L., *Lancet*, 1958, **2**, 1241.
[2] Hill, A. B., Doll, R., Galloway, T. McL., and Hughes, J. P. W., *Brit. J. prev. soc. Med.*, 1958, **12**, 1.

Ectromelus

SIR,—I wish to report a case of ectromelus.

An unbooked Hokien Chinese patient, aged 38 years, with a Sikh husband, was admitted to the Kandang Kerbau Hospital for Women, Singapore, on September 25, 1958. She was unable to remember the date of her last menstrual period and was considered to be about 36 weeks pregnant. She had had three previous normal confinements, each at full term, and gave no history of any illness or abnormality during this present pregnancy.

On examination her general condition was good. A breech presentation was diagnosed, and the foetal heart sounds seemed normal. Labour progressed satisfactorily, and after 10 hours the presenting part appeared at the vulva. A house-surgeon, about to deliver what he thought was a breech with extended legs, was surprised to discover that there were no legs. However, the second stage progressed normally and the baby was delivered without difficulty and was fortunately stillborn. The third stage was normal. The sex of the child was female, and the weight was 4 lb. 10 oz. (2.1 kg.).

Examination of the foetus showed absence of both lower limbs. The left arm and hand were normal, but the right hand had no thumb and first finger and the third and fourth fingers were fused together (Fig. 1). A radiograph of the baby revealed the presence of the upper ends of the femora (Fig. 2). No necropsy was performed.

FIG. 1 FIG. 2

FIG. 1.—Photograph of foetus showing absence of lower limbs and abnormal right hand. FIG. 2.—*X*-ray of foetus showing presence of upper ends of femora.

Gould[1] has classified this type of abnormality as follows: (*a*) Amelus: "a monstrosity without limbs." (*b*) Phocomelus: "a monster with rudimentary limbs, the hands and feet being attached almost directly to the trunk." (*c*) Ectromelus: "a single autositic monster characterized by the presence of imperfectly formed limbs." (*d*) Hemimelus: "a monster with incomplete or stunted extremities."

These conditions are rare and their aetiology still obscure. However, it is now generally recognized that congenital malformations are more often caused by environmental factors during pregnancy than by defective germ plasm. Embryonic tissues are easily damaged by many noxious causes, and quite a number of important congenital abnormalities have been duplicated experimentally in animals. In the case described no evidence for any adverse factor occurring during the pregnancy was obtained.—I am, etc.,

T. WILSON RODDIE.

Department of Obstetrics and Gynaecology,
The University of Malaya in Singapore.

REFERENCE

[1] Gould, G. M., *Medical Dictionary*, 4th edition, edited by R. J. E. Scott and C. V. Brownlee, 1935. H. K. Lewis, London.

Subacute Combined during Liver Therapy

SIR,—My interest in the article by Drs. J. F. Adams and G. C. Timbury (*Journal*, March 28, p. 833) was tempered by the memory of two cases.

Case 1.—J. T., a gardener and cordwainer, died on January 8, aged 85 years, from a myocardial infarction, while working still up to his sudden demise. In 1937 and indeed earlier he had pernicious anaemia with loss of the use of his legs. Consulting Professor F. J. Nattrass in Newcastle, he was ordered large intramuscular injections of "campalon" (Bayer). With the advent of war this was changed to a British liver product. The paralysis disappeared, within months, and while still under the same treatment up to the time of his death he lived a very full life.

Case 2.—C. T., 60-year-old housewife whom a specialist diagnosed three years ago as subacute combined degeneration, has since then been under intensive treatment with vitamin B_{12} and still shows little sign of improvement.

From these two cases one might foolishly deduce that there is something in a good parenteral liver extract which is lacking in parenteral vitamin B_{12}.—I am, etc.,

Hexham. RICHARD BELL.

Venous Shunts in Cirrhosis

SIR,—The many errors in your leading article under the heading "Venous Shunts in Cirrhosis of the Liver" (*Journal*, April 11, p. 963) cannot be allowed to pass. Many of the statistics quoted have long been out of date; it is as if you judged the results of operation for, say, mitral stenosis on the first 20 patients operated upon. Only experience could show the correct criteria in the selection of patients for operation, and surely you are doing a disservice to medicine in basing your report on statistics which do not accord with modern facts. Many of your figures come from the other side of the Atlantic, where the pattern of cirrhosis of the liver differs from that found in this country. It is certainly not true in Great Britain that 50% of patients who bleed die as a result of their first haemorrhage. That the risk of these haemorrhages is considerable is certainly true, and bleeding from varices is now stated in America to carry a higher mortality than bleeding from any other lesion of the digestive tract.

In our own experience of end-to-side portacaval anastomoses for intrahepatic obstruction, amongst the first 100 patients only 4 died while still in hospital, none during the first week after operation. Of the 96 who left hospital 84 are still alive, and 28 of them have been followed for more than 4 years. Two patients died of causes quite unrelated to their liver disease, one died of haemorrhage, and the remainder of other complications of their cirrhosis. Only three of the others have had any serious haemorrhage since their operation. The majority are leading normal active lives. Up-to-date figures from other centres are comparable with these.

The indiscriminate use of any operation will discredit it, and selection of patients together with meticulous technique are the keys to success in this. The neuropsychiatric symptoms to which you refer, and which occur in a minority of patients, are certainly a challenging problem, but in the majority they yield to treatment. The fact is that many of these patients who bleed have only mild cirrhosis which is not progressive, and venous shunt is well worth while, as it will, in nearly all cases, spare them the hazards of repeated haemorrhages. At the moment a group of our patients are being carefully reassessed, and it is evident that in the great majority no varices can be detected a few years after their operation.

Nachlas, on whose paper[1] your leader is based, states that 65% of patients are dead within one year of their first haemorrhage, and that the results of a shunt operation are similar to medical treatment alone. Surgery cannot save a patient who is dying of hepatic failure, but it can prevent those with good or moderate liver function from dying of haemorrhage. The 70% mortality which you quote for portacaval anastomosis applies to a group of patients in whom this operation is contraindicated.—I am, etc.,

Department of Surgery,
University of Bristol. R. MILNES WALKER.

REFERENCE

[1] Nachlas, M. M., *Ann. Surg.*, 1958, **148**, 169.

*** The purpose of the leading article was to draw attention to American views which make this a debatable subject. A further contribution appears in the February, 1959, issue of the *American Journal of Medicine* by L. A. Baker and colleagues. An editorial note on this paper says that "the question [of operative or non-operative treatment] probably will not be convincingly answered, however, until the attempt is made in an appropriately planned experiment on a sufficiently large scale, such as the Veterans Administration has recently undertaken to do."—ED., *B.M.J.*

Needle Biopsy of the Liver

SIR,—Drs. M. Hathorn and N. M. Lamont (*Journal*, April 11, p. 973) draw attention to your rather misleading annotation on needle biopsy of the liver. You conclude with a plea for a quicker biopsy technique and then cite the recent article by Menghini,[1] who gives such an erroneous estimate of the time taken by the Gillman technique. It is strange that your annotator, having referred to the article by Dr. Richard Terry in 1952,[2] should fail to mention Dr. Terry's earlier article[3] in which he described an excellent modification of the Gillman biopsy instrument. With this instrument it is possible to effect a most satisfactory liver biopsy in a minimum of time and with the simplest of movements.

I had the privilege of learning the technique from Dr. Terry, and I am glad to report that his method has been uniformly satisfactory in my hands for a number of years. Those seeking a first-class method of liver biopsy cannot do better than consult the original article and obtain the necessary instrument from W. H. Bailey & Son, 2, Rathbone Place, London, W.1.—I am, etc.,

London, W.1. REGINALD S. MURLEY.

REFERENCES

[1] Menghini, G., *Gastroenterology*, 1958, **35**, 190.
[2] Terry, R., *Brit. med. J.*, 1952, **1**, 1102.
[3] —— ibid., 1949, **1**, 657.

Children in Hospital

SIR,—Your leading article (*Journal*, February 14, p. 425) rightly welcomed the excellent report of the Platt Committee on the welfare of children in hospital. But exception can be taken to its criticism of the committee's balanced views on the separation of the child from its mother. It states: "But many would prefer . . . clearer recognition that separation from his mother alone may prove of serious consequence to the young child." This appears to be a view widely held—e.g., "How seriously and lastingly young children may suffer if separated for even a day or two from their mothers . . . has been abundantly proved" (*Observer*, February 15, p. 14).

This view ignores the fact that there is no single valid investigation to support the statement that separation alone is responsible for emotional disturbances in children. Bowlby's valuable monograph,[1] quoted as evidence in your leading article, is concerned with reviewing the extensive literature which amply demonstrates that deprivation of mothering is harmful to the emotional life of the child. But the greater number of children who are deprived of mothering are in fact living with the mother and are not separated from her. Physical separation of the child from its mother may, or may not, lead to deprivation of mothering. For the mothering the child receives will depend entirely upon the person, or persons, who have the temporary care of it. One investigation[2] has shown that common separations involving the child's stay with friends and relatives is, on the whole, not damaging to the child. Less common separations involving hospital admission were found to be very disturbing. This would appear to show that it is not the separation *per se*, but the circumstances surrounding it which do the damage. We should welcome the Committee's admirable suggestions for minimizing trauma in children admitted to hospital but not condemn separation as an evil in itself.

To emphasize that separation is not harmful in itself is of more than academic importance. By exaggerating the dangers of separation guilt reactions are produced in mothers who have to be separated from their children, and other mothers are discouraged from making use of the prophylactic value of those short periods of separation which naturally are a part of child upbringing. Furthermore, to focus on the fact of separation may divert attention away from the crucial matter, which is that, when separation must occur, care must be taken to supply adequate substitute mothering. In the paediatric ward this involves, above everything, the right selection and deployment of nursing staff.

Some clinical conditions in children notoriously improve on admission to hospital with the consequent separation from their parents. A child grossly deprived of adequate mothering by his mother may benefit greatly, and sometimes urgently requires separation from the mother by admission to a paediatric ward with a "home from home" atmosphere. This is a matter within the experience of those who have to deal with acute feeding difficulties in young children, anorexia nervosa, status asthmaticus, ulcerative colitis, etc., as well as with the emotional disturbances of childhood. An adequate study of how some children benefit from admission to hospital may yield valuable information for developing even more adequate mothering in children's wards.

Finally, many large-scale, beneficial preventive measures are based upon the separation of the child from the parent and the provision of adequate mothering for the child—e.g., adoption, fostering, day fostercare, etc.—I am, etc.,

J. G. HOWELLS.

Department of Child and Family Psychiatry, Ipswich.

REFERENCES

[1] Bowlby, J., *Maternal Care and Mental Health*, 1951. W.H.O., Geneva.
[2] Howells, J. G., and Layng, J., *Lancet*, 1955, **2**, 285.

"Disipal"

SIR,—In "To-day's Drugs" (*Journal*, March 14, p. 714) you state that "disipal" (orphenadrine hydrochloride) is similar in its effects in the treatment of Parkinsonism to those of diphenhydramine and benzhexol ("artane," "pipanol"). Disipal has been shown to be a far more effective drug than artane.

In a recent survey[1] of 398 patients attending my Parkinson's Disease Clinic in May, 1958, disipal was found to be the most effective drug used in 86 (21.6%) of these patients as compared with 20 (5.3%) taking artane. Furthermore, artane has been demonstrated to cause mental symptoms[2] in a certain number of patients when used in effective doses for the treatment of Parkinsonism. Disipal has never been known to cause distressing mental symptoms. It has a well-known euphoric effect, and preliminary investigations strongly suggest that disipal is useful in combating dizziness both of the Ménière's type[3] and the post-traumatic kind.[4 5] Further trials are in progress. There is also some recent evidence[6] that disipal is effective in relieving low back pain when there is muscle tension present, a property not possessed by artane.—I am, etc.,

Dudley Road Hospital, Birmingham, 18. R. O. GILLHESPY.

REFERENCES

[1] Gillhespy, R. O., *Indian Practit.*, 1958, **11**, 567.
[2] Porteous, H. B., and Ross, D. N., *Brit. med. J.*, 1956, **2**, 138.
[3] Duursma, S., *Med. Tms (N.Y.)*, 1958, **86**, 573.
[4] Havinga, H., *Ned. milit. geneesk. T.*, 1958, **11**, 187.
[5] *Brit. med. J.*, 1959, **1**, 773.
[6] Goodley, E. L., *Gen. Pract. Clin.*, 1958, **20**, 14.

Steroid Metabolism in Congenital Adrenal Hyperplasia

SIR,—Dr. C. L. Cope (*Journal*, March 28, p. 815) has, by a nice combination of steroid chemistry and deduction, established in his patient with congenital adrenal hyperplasia that hydroxylation must be occurring in the C 11, 17, and 21 positions. He concludes therefore that the defect in his patient is but partial, and this conclusion has been reached before by other observers.[1]

Congenital virilizing adrenocortical hyperplasia is in fact a syndrome in which there are not only varying degrees of androgen excess but also varying degrees of deficient hydrocortisone production. He finds these facts inconsistent with the Bongiovanni–Eberlein hypothesis[2] that there

is a compensatory hyperplasia of the adrenal cortex in order to produce sufficient hydrocortisone for the body's needs, but his own case demonstrates quite clearly that this has occurred with a 20-times the normal quantitative output of adrenocortical steroids in the urine.

Dr. Cope's hypothesis leaves him, not just with a chemical problem as he suggests, but also a clinical problem which he does not mention. He has not only to discover where the urinary excretion of 4.4 mg. of tetrahydrocortisone and tetrahydrocortisol (70% of the minimum daily secretion rate in young women by his calculation) is coming from, if it does not derive from hydrocortisone breakdown, but also to decide how his patient managed to avoid a state of adrenocortical insufficiency in the presence of a plasma-hydrocortisone level which Dr. Abelson reported to be no more than one-tenth of the mean normal.

Clearly both the Bongiovanni–Eberlein and the Cope hypotheses are correct, but a further hypothesis is required to resolve their apparent differences and to explain the clinical facts. Such a hypothesis is found in an increased rate of peripheral utilization of hydrocortisone which could explain both the state of eucorticism enjoyed by the patient and the near normal output of hydrocortisone derivatives in the urine, despite an extremely low plasma level. *When the urinary output of hydrocortisone derivatives fails to correlate, either with the level of plasma hydrocortisone or with the clinical state of the patient, an abnormal rate of peripheral utilization must be considered.*

When this principle is applied to the solution of those clinical and chemical difficulties which remain in our understanding of congenital virilizing adrenocortical hyperplasia it may be objected that the use of cortisone in treatment is not accompanied by a "Cushing-like" reaction in the patient and that the levels of the urinary metabolites are no greater than would be expected from the amount of cortisone which is being given. This is true, and the hypothesis therefore requires a further assumption that it is the high level of circulating androgens which determines the enhanced rate of tissue utilization of hydrocortisone; when the androgens fall to normal levels with cortisone therapy the rate of peripheral utilization also falls.—I am, etc.,

DOUGLAS HUBBLE.

Department of Paediatrics and Child Health, University of Birmingham.

REFERENCES

1 Hubble, D. V., and Illingworth, R. S., *Arch. Dis. Childh.*, 1957, **92**, 297.

2 Bongiovanni, A. M., and Eberlein, W. R., *Pediatrics*, 1958, **21**, 661.

Diabetes in the Tropics

SIR,—Your leading article on "Diabetes in the Tropics" (*Journal*, January 24, p. 219) prompts me to report the following case:

A European male, aged 29, eight years' resident in Singapore, consulted me on February 12, 1959, complaining of 17-lb. (7.8-kg.) loss in weight in the previous two months, accompanied by thirst. He had noticed that he had had to rise to pass urine once during the night for the past year. He had no illness during the previous year apart from a cough and feverish cold for four days in October, 1958. He appeared fit, of normal build, height 5 ft. 8 in. (1.7 m.), weight 167 lb. (76.2 kg.), and there were no abnormal physical signs. Routine *x*-ray of chest on February 8 had been normal. Urine showed brick-red reduction of Benedict's reagent. A glucose tolerance test on February 18 showed a fasting blood sugar of 180 mg./100 ml., rising to 240 mg./100 ml. half an hour, 260 mg./100 ml. one hour, and 240 mg./100 ml. two hours after glucose. Fasting urine contained 1% glucose, inferring a lowered renal glucose threshold, half-hour specimen contained 1%, and the one-hour and two-hour specimens both contained 2% glucose. All urine specimens were acetone free.

The patient was told to avoid sugar and reduce his intake of carbohydrate. He was commenced on 0.5 g. tolbutamide twice daily. Two days later, as his urine was sugar-free, this was reduced to 0.25 g. tolbutamide twice daily. He remained sugar-free, his weight remained steady, and his polyuria disappeared. Two weeks later the tolbutamide was reduced to 0.25 g. each evening. As he still remained sugar-free the tolbutamide was stopped after a further five days. After being eleven days off all tolbutamide treatment, a glucose tolerance test on March 24 showed a fasting blood sugar of 80 mg./100 ml., rising to 120 mg./100 ml. half an hour, 160 mg./100 ml. one hour, and 100 mg./100 ml. two hours after glucose. All specimens of urine were free from glucose and acetone. The patient feels fit and the weight has remained unchanged.

It is becoming generally acknowledged in this area that Asian diabetics frequently show amazing returns to normal blood sugar curves after a short period of tolbutamide or insulin treatment. I feel that it is worthy of note that it now appears that Europeans living in the tropics also seem to have this power of recovery from diabetes mellitus. If, therefore, this temporary diabetes with, as in this case, no obvious cause really does not occur in temperate climates, then it infers that the tropical environment either causes a temporary form of diabetes or alternatively enables recovery from classical diabetes to take place.—I am, etc.,

Singapore, 1. W. B. WADDELL.

"Poisoning" by Tolbutamide

SIR,—Professor D. M. Dunlop (*Journal*, March 28, p. 857) criticizes my heading of a description of the serious ill-health of a patient on tolbutamide as poisoning and not possible or suspected poisoning. I used the bare title deliberately as I wanted, and thought it advisable, to shake the attitude I have found so common in its use in diabetes. Well, if it proves to do no good in this case, at least it does no harm. This medical attitude may not be so common with Scottish practitioners, and so Professor Dunlop, whose opinion I respect enormously, may not have to deal with such implications.

Whether our disagreement about tolbutamide is more than verbal I should like to know. He and his workers in Edinburgh were the first to recognize toxicity from carbutamide, and from these cases, and others transferred and treated with tolbutamide, must have a large experience of any or relative toxicity which I am sure those anxious to try oral treatment of diabetes would like to know, and I wish he had mentioned this in his letter.—I am, etc.,

London, W.1. R. D. LAWRENCE.

Smog

SIR,—I, like many more of my colleagues, have been working night and day during the recent lethal and prolonged spell of smog. I am not complaining about the extra work, but about the tragic and pathetic plight of many of our elderly patients gasping for breath and relief from the painful body-racking and exhausting coughing, etc.

Whenever smog strikes us, all we hear and read about in the national press is the tremendous financial loss to business and industry. But what about the loss of human life? Judging by the attitude of those concerned it would

appear that the cheapest commodity is human life. Ironically enough, the use of poison gas in wartime has been outlawed by the Geneva Convention, but what in the name of common sense is smog if not a poison gas being used indiscriminately in peacetime? We shout from the roof-tops all about "preventive medicine," yet when we know of the many illnesses following an attack of smog we do nothing about preventing them. This is surely stark insanity. We boast of having one of the finest health services in the world. We spend prodigious sums of money to try to reach the moon, and create the most costly, destructive, and fiendish weapons of war. We do all in our power to increase the span of life, yet at the same time how little we do to look after these same people.

To solve the problem the powers that be suggest smokeless zones—but apart from conversion into smokeless zones of an odd square mile of city here and there and feeble appeals to the public to convert to modern fireplaces which would reduce the smoke element and smog, what have the authorities really accomplished? Nothing. From the Government's point of view the question of doing away with smog is primarily one of money, and judging from their inactivity it would therefore appear that they are more concerned with the saving of pound notes than human lives.

What about the medical profession—is our conscience clear? Apart from advising old people to remain indoors during smog, what else have some of our officials really done? Apparently nothing! We want real action from them, not a lot of childish talk, statistics, and sentimental slush. It is all very well advising the old folk to stay indoors (as if they don't know that themselves), but who is going to do their shopping for food or other life-sustaining necessities? Must they now die of starvation, lack of heating, as well as smog? Surely it is the duty of all medical men, including the family doctor, to hit out at officialdom in every conceivable way until the ghastly menace of smog has been completely banished from our midst.—I am, etc.,

ARNOLD B. COWAN,
Honorary Life President,
The Glasgow and West of Scotland
Old Age Pensioners Association.

Glasgow, S.W.3.

Monilial Granuloma

SIR,—I was very interested to read the paper of Dr. K. Nityananda (*Journal*, March 14, p. 690), describing a case of monilial granuloma of the scalp, and pointing out the rarity of the condition. I have recently had a similar case under my care which was shown at the meetings of the Paediatric Section of the Royal Society of Medicine in Bristol in 1958, and the South-west of England and Wales Society of Dermatology in Bristol in February, 1959.

A female child, aged 5½, had, when 2 weeks old, moniliasis in the buttock area, and at this time she was also noticed to have moniliasis of the mouth which has persisted up to the present time in spite of various local treatments. Two years ago she developed crusted horns round the scalp and ear (see photograph). These were curetted off one year ago but gradually re-formed.

For the past two to three years a productive cough has been noted and examination shows clubbed finger-nails. *X*-rays of the chest showed increased shadows at both bases. No abnormality was demonstrated by bronchograms. Bronchoscopy showed pus in the bronchi and a papilloma in the inter-arytenoid fold. Her haemoglobin was 68% and the film showed iron-deficiency changes. Serum calcium 9.9 mg./100 ml. Glucose-tolerance curve normal. *Candida albicans* was demonstrated in mouth-scrapings, in sputum removed at bronchoscopy, and in the skin crusts. Histology of skin and laryngeal papilloma showed chronic inflammatory granulation tissue. Large amounts of

mycelial filaments and yeast bodies were present in the skin crusts and in the superficial tissues in the laryngeal papilloma.

The scalp condition almost completely cleared after a period of three months in hospital, during which time her general condition improved, the anaemia was corrected, and nystatin ointment used locally. In addition she also inhaled nystatin as an aerosol three times per day, and, as judged by the amount of sputum, her chest condition has improved considerably.

One cannot help feeling that in such cases there is some biochemical change in skin and mucous membranes which allows monilia to grow more readily. In this connexion Dr. G. Wells informed me that the case reported by Hauser and Rothman,[1] as quoted by Dr. Nityananda, later developed diabetes. As pointed out by these authors, the condition is very serious, and the four cases in the literature who were followed up all died in childhood.—I am, etc.,

ROBERT P. WARIN.

Bristol

REFERENCE

[1] Hauser, F. V., and Rothman, S., *Arch. Derm. Syph. (Chicago)*, 1950, **61**, 297.

"Medrone"

SIR,—In "To-day's Drugs" (*Journal*, April 4, p. 919) it is stated that "medrone" (methylprednisolone) is nearly twice as potent as prednisolone and that doses of the latter should be approximately halved to calculate the dosage of medrone. Although this potency relationship has been demonstrated in the laboratory,[1] most published reports indicate that medrone is 1¼ to 1½ times as potent as prednisolone when used clinically. In general there is a more favourable potency relationship in the allergic diseases than in rheumatoid arthritis.[2]

It must be pointed out that we do not claim that medrone is twice as potent as prednisolone, but that it is 1¼ to 1½ times as potent. The following quotation from a recent report[3] summarizes the matter both adequately and accurately:

"The claim made by the manufacturers that medrone is approximately 25% more potent than prednisolone appears to be justified, and, since the drug is marketed in a strength of 4 milligrammes, this allows a tablet of medrone to be substituted satisfactorily for one of prednisolone."

Adequate dosage of steroids is all-important, particularly so when a transfer is made from one steroid to another. For this reason, it must be understood, when a transfer is made from prednisolone to medrone, that this should be on a tablet for tablet basis;

also that for practical purposes a 4-mg. tablet of medrone is equipotent with a 5-mg. tablet of prednisolone.—I am, etc.,

A. R. H. HICKS,
Medical Adviser,
Upjohn of England Ltd.

Crawley, Sussex.

REFERENCES

1 Dulin, W. E., Barnes, L. E., Glenn, E. M., Lyster, S. C., and Collins, E. J., *Metabolism*, 1958, **7**, 398.
2 Feinberg, S. M., Feinberg, A. R., Pruzansky, J., and Fisherman, E. W., *J. Amer. med. Ass.*, 1957, **165**, 1560.
3 Montgomery, D. A. D., *Ulster med. J.*, 1958, **27**, 130.

Personal Medical Record Disks

SIR,—In Dr. H. J. Parish's article (*Journal*, March 7, p. 640) a medical record disk (in Fig. 2) shows a child of 10 as having a "National Insurance Number" whereas the letters and figures indicate it to be a "National Health Service Number."

Although such a scheme might be very useful in certain special circumstances, I think that in this country it would be cheaper and much more appropriate if such information as Dr. Parish suggests was recorded *concisely* on each individual's N.H.S. record. At present the back of the record envelope (E.C. 5 and 6) serves as the first continuation card and is soon filled with details of the child's first trivial illnesses, which remain in this prominent position for the next 50 years or so.

Surely the Ministry of Health should arrange at once for the back of the envelope to be left blank in all future printings, except perhaps for the words "This space should be used to enter important medical information only." It will take many years before a significant proportion of the envelopes bear this modification. In the meantime printed gummed labels could be available to those doctors who wish to cover up the out-of-date notes and convert at once to the new system.

In due course some committee could decide on the best layout of the back of the envelope, but I suggest it should be kept very simple. A pair of vertical rulings for year and major diseases and operations on one half of the page, and a similar pair on the other half for year and immunizations, blood group, drug sensitivity, etc., might be all that are necessary. To save space, only completed courses of immunizations would be recorded here, although full details of each injection would appear on the current continuation card inside.

I am sure many patients imagine that something like this is done already, and they often think it unnecessary to tell us of their past history even if they are new to us. They certainly would not think they had to remind us of a drug sensitivity at each visit, but this could easily be overlooked on a quick glance through several continuation cards, with serious consequences.—I am, etc.,

K. SOUTHGATE.

Brill, Bucks.

Medical Ethics

SIR,—I feel that the letter from Dr. T. C. Dann (*Journal*, April 11, p. 975), referring to the recent operation on the Siamese twins at St. Bartholomew's Hospital, should not be allowed to pass without comment. It seems to me to be both cynical and pointless, as he has nothing but destructive criticism to offer in taking up the cudgels on behalf of people who are apparently quite content to accept the present order of things.

Presumably the parents of the twins are not demanding strict secrecy over the progress of their two sons. The public who read or hear about them are not the casual gossipers that Dr. Dann seems to imply, but consist largely of people who are genuinely concerned for both the central figures in this somewhat unusual drama. Many people are finding it a moving experience to hear of Jeremy and Timothy in the context of international affairs on the news: what is it after all but the struggle for existence on a so very much smaller scale?

Fathering and mothering children who start life with a handicap they may or may not be able to overcome are unquestionably heavy responsibilities, but it reflects a cynical approach to life to describe the advent of such children as "always good news for the papers, although rarely so for the parents."

As to the publishing of names of the doctors concerned, members of a surgical team are normally content to remain anonymous outside the hospital in which they work. The final slur on the morals of those concerned with the case is too petty for comment. A member of the profession which is striving so hard to help one, if not both, of these youngsters through to a normal and happy life would have done better to refrain from this type of criticism of colleagues so very much more experienced and responsible than he himself appears to be.—I am, etc.,

DOROTHEA M. WIGFIELD.

South Harrow, Middlesex.

SIR,—The ill-advised letter of Dr. T. C. Dann (*Journal*, April 11, p. 975) appears to be another example of people living in glass houses. Overenthusiastic defence of a principle often leads well-intentioned people to the very fault they seek to condemn. Dr. Dann will probably realize in retrospect with regret that the last sentence of his letter is in itself an unfortunate breach of good taste and contrary to accepted medical ethics.

His letter has received widespread notoriety in the popular press and is liable to be misconstrued as implying that the consultants concerned had not given sufficient credit to all the other people concerned, whereas in fact the prosaic statement issued by the hospital authorities merely stated that the ultimate direction of the whole manœuvre lay in their hands. It would be a gracious gesture if Dr. Dann were to issue a public disclaimer of any such intention and might repair some of the damage caused by his unfortunate and undignified letter.—I am, etc.,

P. D. A. DURHAM.

Ryde, Isle of Wight.

The Ashton-under-Lyne Siamese Twins

SIR,—The publicity given to this case by the Press has been without my knowledge or authority, and the information derived from the *x*-ray films and the radiologist's report was divulged to the Press before I myself had been shown either, and without consideration for the interests of the patient and her relatives.

I should be grateful if you would publish this statement of the facts in your columns.—I am, etc.,

F. A. L. DA CUNHA.

Manchester, 3.

POINTS FROM LETTERS

Foreign Body in the Nose

Dr. L. G. JACOB (Bracknell, Berks) writes: An instrument which can be used in the same way as a hairpin (*Journal*, January 31, p. 302) and has the advantage of a firm handle is a curved perichondrial elevator. It can also at times be used for a foreign body in the ear.

Dr. R. J. HARLEY-MASON (Nairobi, Kenya) writes: In your issue of January 10 (p. 115), Dr. P. D. Sparke describes an ingenious method of removing a foreign body from a child's nose, which, however, is inapplicable to the ear. May I suggest another method applicable to both? I have many times used a vectis for this purpose, and cannot remember ever having had a failure with it.

Obituary

E. FARQUHAR MURRAY, M.D., F.R.C.S. F.R.C.O.G.

Professor E. Farquhar Murray, emeritus professor of midwifery and gynaecology in the University of Durham and honorary consulting gynaecologist to the Royal Victoria Infirmary, Newcastle upon Tyne, died suddenly at his home at Newcastle on March 23. He was 73 years of age.

Ernest Farquhar Murray was born on January 13, 1886. Educated in his home town of Dundee, he graduated M.B., Ch.B., with honours, at St. Andrews University in 1908, proceeding to the M.D. three years later. After holding the posts of house-physician, house-surgeon, and out-door obstetric assistant at the Royal Infirmary, Dundee, he came down to London to be house-physician at the Children's Hospital, Paddington Green, and resident medical officer at the Chelsea Hospital for Women and at Queen Charlotte's Hospital. When the first world war began in 1914 he joined the Royal Navy and served throughout the hostilities.

After a period at Chatham Hospital he joined H.M.S. *Caroline*, and for his services at the Battle of Jutland was mentioned in dispatches. He maintained an abiding interest in the Navy and continued to serve in the R.N.V.R., attaining the rank of surgeon commander. In 1918 he took the Fellowship of the Royal College of Surgeons of England, and then held the post of registrar and pathologist at the City Road Lying-in Hospital in London.

Moving to Newcastle upon Tyne in 1921, Farquhar Murray became honorary assistant gynaecologist to the Royal Victoria Infirmary and honorary obstetrician to the Princess Mary Maternity Hospital, and the University of Durham appointed him lecturer. He was a foundation Member of the Royal College of Obstetricians and Gynaecologists, and served on its first council. In 1931 he was elected to the Fellowship of the College, and again served on its council for a further period of nine years. When Professor R. P. Ranken Lyle retired in 1935 Farquhar Murray was appointed to the senior posts at the hospitals and to the chair of midwifery and gynaecology in the university. His brother, the late Professor Leith Murray, had held a similar chair at the University of Liverpool. Retiring from his clinical appointments in 1946, Professor Farquhar Murray gave up his university post in 1951. Among the hospitals which he served were the Cameron Hospital, West Hartlepool, the Ingham Infirmary, South Shields, and the Durham County Hospital.

A member of the British Medical Association for fifty years, he was honorary secretary of the Newcastle upon Tyne Division from 1921 to 1927 and chairman of the Division in 1930–1. When the Association held its Annual Meeting at Newcastle upon Tyne in 1921 he acted as one of the honorary secretaries of the Section of Obstetrics and Gynaecology, and at the Glasgow Meeting in 1922 and at the Oxford Meeting in 1936 he served as a vice-president of the same Section.

F. E. S. writes: The bare bones of the career of a man so vital as Farquhar convey little of his real influence in the world and in his profession. He had a mind of quicksilver, a wit that sparkled, and a presence that justifiably conveyed an air of distinction. At work he loved speed, and as his plodding house-surgeon I well remember his 4¼-minute ectopic, his 6-minute caesarean, and his attempt to complete three Wertheim hysterectomies in a forenoon. He was a "character" in a time when characters were becoming scarce. Students loved him and his ways, and when he retired from the chair he received the unique distinction of a presentation from the class of the year. He was so volatile and hasty in temperament that he could easily give offence, but no one could bear Farquhar ill-will for long—he was too ready to admit his own human fallibility.

Like all characters he gave rise to many stories, and perhaps the most revealing is the occasion when he was walking along a hospital corridor with the writer. In front of us walked a very senior and highly respected member of staff. Quoth Farquhar: "Poor old X. What an existence—must never have done anything wrong in his life." For long he was a member of the Gynaecological Visiting Society, and it is an understatement to say that he enlivened all their meetings. He loved to puncture pomposity. In spite of his apparent flippancy and mercurial reactions he could shrewdly assess the worth of any man, student or professor.

His greatest contribution to our art was his conception of the obstetric flying-squad, and for this he will always be remembered. His enthusiasm was such that he inspired all his colleagues, and it soon became apparent that the lives of mothers and babies were being saved. Now, with flying-squads operating all over the British Isles and in many other parts of the world, it can truthfully be said that thousands owe their health and their lives to Farquhar Murray. He greatly admired and was devoted to his elder brother, Leith Murray, of Liverpool, and when Farquhar was faced with a difficult task he often sought Leith's counsel.

Soon after he qualified Farquhar went to the Far East as a ship's surgeon, and so impressed was he by the value of such a journey that he recommended all his newly qualified graduates to seek a similar engagement. As a result a large number of Durham graduates went on foreign trips, and Farquhar was very proud of the large and flourishing Blue Funnel Club that meets at dinner annually in Newcastle and to which some of the most famous explorers, travellers, and members of the Services have come as guests. After he retired he again enrolled as a ship's doctor and travelled once more his old route to Malaya, Sumatra, and Japan.

Soon after he retired he suffered a slight cerebral accident. This threw him into a panic—a panic not that he might die but that he might be crippled and be a burden to himself or to others. Fortunately he recovered well enough to continue taking an interest in his profession and in his friends. One could not cease to admire the gallantry with which he disregarded his disability. When many men would have needed the help of a stick or would have sat quietly at home Farquhar continued to go out to medical meetings and social occasions whatever the strain entailed. A few hours before he died he had been on the top of his form with quip and joke.

He leaves a brother, Dr. Cecil Murray, and a charming and devoted wife, Madge. Many who read this must have enjoyed her hospitality, and with her we mourn the loss of a brilliant, accomplished, and lovable man.

A. A. BISSET, M.D.

Dr. A. A. Bisset, who was in general practice at Sheffield and later at Harrogate, died on March 23 while watching the National Hunt steeplechase at Aintree, two days before his 74th birthday.

Alexander Andrew Bisset was born at Knockando, Banffshire, on March 25, 1885, the son of a well-known breeder of Aberdeen Angus cattle. Graduating M.B., Ch.B. with honours at Aberdeen University in 1908, he proceeded to the M.D. two years later. Soon after graduation he went to Sheffield to become an assistant in a partnership with Dr. E. W. D. Kite and Dr. E. Bruce Wilson. Ultimately he

became principal of a very extensive practice, but in 1926 a breakdown in health compelled him to leave Sheffield. He then went to live at Dulwich, where he practised for a short time before going abroad for further study, working at the Mayo Clinic and in Vienna and Paris. He settled at Harrogate in 1928, and here again he showed his ability to build up a very widespread practice. Indeed, in the last six years of his life he found it necessary to have rooms in Wimpole Street to deal with his patients from the south of England. His main interest was in rheumatism, and he was a member of the International Society of Medical Hydrology. He served in East Africa and England during the first world war, and was seconded to the Royal Flying Corps, from which he retired with the rank of major. It was from this contact that he became one of the founder members of the Royal Air Force Club in Piccadilly. He took a great interest in sport, and was a well-known shot and a great man for salmon fishing and racing. He leaves a widow, a son, and a daughter, to whom we extend our warmest sympathy. His son is in medical practice in London. —G. N. B.

DEBABRATA CHATTERJEE, M.B., B.S.

Dr. Debabrata Chatterjee, who had been a senior house officer in thoracic surgery at Grove Park Hospital, London, died suddenly on April 1, at the early age of 31.

Debabrata Chatterjee was born on February 2, 1928, and studied at the Medical College, Calcutta, graduating M.B., B.S. in 1953. Thereafter he worked for some three years in his teaching hospital, first as a junior medical officer and later as a junior house-physician, specializing in paediatrics, and later was promoted to senior house-physician by his professor. His work was held in extremely high regard in his hospital and medical school, and he decided in 1957 to specialize in general medicine with an emphasis on diseases of the chest, and came to Britain to gain more experience. He worked at Grove Park Hospital first as house-surgeon in the thoracic surgery department and later as registrar on the medical side. He then proceeded to Edinburgh to study for the higher diploma of M.R.C.P., during the course of which he was unfortunately stricken with the severe illness from which he died.

M. M. N. writes: It is as a young man of charm, education, and honesty of thought and purpose that Chatterjee will be long remembered. During his short time in this country he made many friends and was extremely well liked by his patients and colleagues, senior and junior. Even during his illness his mind was never at rest, but constantly searching for new fields to conquer. He began to learn French, and found he would work well with his hands and began to develop several hobbies. His death is a great loss to those who knew him and worked with him, and we offer our deepest sympathy to his father and younger brother at this grievous time.

C. O. HUDSON, M.R.C.S., L.R.C.P.

Dr. C. O. Hudson, who was in general practice in Sheffield for nearly 40 years, died at his home in that city on April 3. He was 68 years of age.

Born on July 19, 1890, the son of Dr. Osborne Hudson, Claude Osborne Hudson was educated at St. Bees School and at Sheffield University. His student career was interrupted by the first world war, at the beginning of which he enlisted as a combatant. He served as an officer in the Royal Field Artillery, much of his time being precariously spent as a forward observation officer. In 1916 higher authority discovered that he was a medical student and he was sent back to England to continue his studies. After qualifying M.R.C.S., L.R.C.P. in 1919, he held the post of house-physician at the Sheffield Royal Infirmary, and then entered general practice in the city. He became also medical officer to the Treasury. Dr. Hudson immediately re-enlisted, this time in the R.A.F., at the outbreak of the second world war, throughout which he served in an administrative capacity, attaining the rank of wing commander. In 1940 he suffered the tragic loss from enemy action of his older daughter, who was serving in the W.A.A.F. His wife, formerly Miss Bertha Schofield, died in 1958, and he is survived by his second daughter.

E. W. S. writes: Throughout his many years in general practice Dr. C. O. Hudson showed an unusual capacity for work, combined with a rare ability to win affection from his patients and his colleagues. He lavished particular care upon the elderly and made it his business to spend much time with them. When confronted with a problem he had a happy knack of getting quickly to the root of it with a direct attack, avoiding all side issues, and he was usually right. The increasing demands on his time were unstintingly and quietly met, and he was one of Sheffield's outstanding practitioners. His particular hobbies were motoring and Sheffield plate: he had a wide knowledge of the latter and was reputed to possess one of the finest private collections in the country. His later years were much dogged by ill health, which he bore with good humour and insight. It was probably characteristic of the man that, all too soon after escaping from the care of the surgeons, he recognized the symptoms of his last illness while opening the garage doors as he set out on an emergency visit.

R. J. PERCY THOMAS, M.R.C.S., L.R.C.P.

Dr. R. J. Percy Thomas, who was in general practice at Plymouth for some 40 years; died on April 6 at Wellington, Somerset, where he had been living in retirement. He was 79 years of age.

Robert John Percy Thomas was born at Llandrindod Wells on May 12, 1879, and was educated at Newton College, Newton Abbot, Devonshire. Receiving his medical training at St. Bartholomew's Hospital, he qualified M.R.C.S., L.R.C.P. in 1903, and then held the appointment of casualty officer at the London Temperance Hospital in 1903–4. Soon afterwards he settled in general practice in Plymouth, where he remained until he retired in 1946. During his active career he was chairman of the Plymouth Division of the British Medical Association in 1925–6, president of the Plymouth Medical Society, and a member of the panel committee. Although not long after his recovery from a serious illness, he conducted a large general practice during the years of the second world war, and served regularly on medical recruiting boards. A man of a quiet, kindly disposition, he was much beloved by his patients, and held in high esteem by his colleagues. He was well known for his skill in shooting and fishing, often visiting the neighbourhood of Looe, Cornwall, for those sporting pursuits. He leaves a widow and one daughter, to whom our sincere sympathy is extended.

R. W. HARTE, M.B., B.Ch.

Dr. R. W. Harte, who was in general practice at Macclesfield, Cheshire, for over twenty years, died in his sleep at his home at Fallibroome on April 8. He was 59 years of age.

Robert William Harte was born on August 27, 1899, and studied medicine at Trinity College, Dublin. After graduating M.B., B.Ch. in 1925, he held the appointments of house-surgeon at Drumcondra Hospital and external assistant at Coombe Hospital, Dublin. He then practised for some three years at Enniscorthy, Co. Wexford, before moving to Seven Sisters, near Neath, Glamorganshire. In 1937 he settled in Macclesfield, where, by his industry and hard work, he built up a very good practice. He became also medical officer to the Lyme Green Paraplegic Settlement, whose inmates in particular have cause to regret his death. An active member of the British Medical Association, he was chairman of the Macclesfield and East Cheshire Division in 1954–5. He had also served on the local medical committee for Cheshire.

F. E. L. writes: Dr. Robert W. Harte was representative of the best type of general practitioner. He had good

clinical acumen, and nothing was too much trouble for him where his patient's advantage was concerned. Possessing himself a high standard of medical ethics, he was intolerant of those who were careless in these important matters. He was in the truest sense the family physician to whom his patients could turn in their troubles, not always medical, confident that they would find sympathy, understanding, and help. For many years he had been divisional surgeon to the St. John Ambulance Brigade, and in Macclesfield he was instrumental in obtaining for the association a headquarters which was the envy of other divisions in Cheshire. In 1952 he was honoured by being made Officer Brother of the Grand Priory in the British Realm of the Most Venerable Order of the Hospital of St. John of Jerusalem. A keen sportsman, he had played rugby for Trinity College before taking up golf, at which he spent his leisure hours. He was a true and loyal friend who will be sadly missed, by none more than the writer of this tribute. To his widow and three children we extend our deepest sympathy.

W. J. STUART, C.B.E., M.B., F.R.C.S.

J. R. M. writes: I have just read your obituary (March 7, p. 652) of dear old "Pussy" Stewart, of Edinburgh, and hope you can find space for a further brief tribute. I was his house-surgeon in the Deaconess Hospital for six months in 1922. The inspiration of his example was only equalled by the patience with which he steered my course in all surgical work. It so happens that last summer I went on a cruising holiday at the same time that "Pussy" went fishing in Tobermory. I did not, however, learn that he was there until 10.30 at night, but with his usual courtesy and hospitality he saw me in his bedroom, and I was amazed at his wonderful memory. It was sad to see him so frail, but he was as cheerful and kindly as ever.

Medico-Legal

CANCER IN ATOMIC ENERGY EXPERIMENTAL OFFICER

In December last the Manchester coroner held an inquest on a 28-year-old assistant experimental officer employed by the Atomic Energy Authority who died of cancer. The experimental officer had worked at their Springfield Factory, near Preston, from August, 1950, until his death in November, 1958, and during the whole of that time, except for about a year, he worked with radioactive materials. He was engaged in general chemical and spectroscopic examination of raw materials and uranium compounds.

In 1955 he married, and his wife said that during their married life he had always been active and healthy until about the middle of November, 1958. On November 14 a sudden attack of abdominal pain compelled him to visit the works medical officer. He complained of increasing pain of three days' duration in the right inguinal region and nausea that morning. He was tender in the right inguinal region and round the umbilicus. He was sent home, and seen the next day by his own doctor, who diagnosed severe gastritis or gallstones. On November 17 he was admitted to Victoria Hospital, Blackpool, and his wife was later told that he had cancer of the liver. On November 29 he was admitted to the Christie Hospital, Manchester, but died the next day.

Post-mortem examination showed that the immediate cause of death was peritoneal haemorrhage from a large secondary deposit in the liver. There were smaller deposits in the lungs, pancreas, and lymph nodes, but the primary growth was in the right testis, which was enlarged and replaced by a white cystic tumour. Microscopy showed this to be a chorion carcinoma arising in a teratoma. The bone marrow and the left testis were normal and did not appear to have been affected by radiation. The right testis was not tested for radioactivity. In the opinion of the pathologist who performed the post-mortem examination at Christie Hospital death was from natural causes, and the employment at an atomic energy factory just coincidental.

Evidence was given at the inquest that before entering the employment of the Atomic Energy Authority the experimental officer had a medical examination, which included a thorough physical examination, blood analysis, and chest radiograph. No family history of cancer was elicited. All employees were offered a re-examination each year, and this officer was, in fact, examined each year except 1953 and 1956. His last examination was on July 18, 1958. Additional blood counts were taken as a routine. No significant abnormality was found on any occasion. Evidence was also given about the precautions against radiation taken at the Springfield Factory. These included the wearing of personal protective clothing, personal and plant cleansing, and plant inspections. Every exposed employee wore a photographic monitoring film to check his exposure to radiation, and this was recorded. The maximum permissible dosage for employees was laid down as not more than 5 roentgens per annum for gamma radiation and not more than 15 rad per annum for beta radiation. In fact, the cumulative totals recorded on the experimental officer's films during his eight years' employment were for gamma radiation 1.63 roentgens and for beta radiation 2.06 rad.

Mr. T. G. J. Clinton, a chief chemist for three years with the Atomic Energy Authority, said he knew of no other case of cancer occurring during the time he had been at the Springfield Factory. Dr. A. Butterworth, a health and safety manager of the Atomic Energy Authority, said that he had never come across this type of cancer in connexion with ionizing radiation.

The Coroner's jury found that the cause of death was that stated in the medical evidence. They returned a verdict of "Natural Causes." No rider was added.

Medical Notes in Parliament

CRITICISMS OF CONSULTANT SERVICE

Part-time appointments, merit awards, pay-beds—all these aspects of the consultant service were brought out and gone over again in a half-hour debate between midnight and one o'clock on April 15, which Mr. D. H. HOWELL (Birmingham, All Saints, Lab.) and Mr. RICHARD THOMPSON, Parliamentary Secretary, Ministry of Health, shared between them.

Part-time Versus Whole-time Appointments

Mr. HOWELL first questioned the trend towards maximum part-time service from whole-time service. At the end of June, 1955, there were 3,166 whole-time consultants, and at the end of September, 1957, only 26 more. The explanation for so small a net gain must be that there had been a considerable loss in the change-over to part-time service. Regional boards and management committees were encouraging the change-over. That was regrettable. From time to time there were complaints about part-time consultants of their laxity in ward rounds and in out-patient visiting, and that domiciliary visits were abused. One reason for encouraging the change to part-time service was that it was felt right to give consultants the opportunity of earning private fees. That would appear to be introducing a salary increase by the back door.

The Birmingham Regional Hospital Board obtained an opinion from counsel that a change from whole-time to part-time service constituted fresh terms and conditions of service. Regional hospital boards had been pressed by the Ministry into disregarding that legal opinion. The more full-time specialists in the Health Service became maximum part-time, the more pay-beds were required for them to

bring their private patients into hospital to receive priority treatment. This was a disturbing trend, because it meant that people were treated not on the basis of their need of treatment but could buy priority in medical attention.

"Buying Priority"

From the general he turned to the particular. Recently the West Bromwich Executive Council had stated that a child on the normal waiting-list for a tonsils operation had to wait a considerable time, whereas if the parents were prepared to pay a handsome fee the child could be taken into hospital almost overnight. People who wanted to enter teaching hospitals in Birmingham had to join a long queue, but if they were prepared to pay 20 guineas a week they could get in almost the next day. Nobody could justify that on ethical grounds.

He recited "a glaring example" given him by another Birmingham M.P., Mr. Charles Howell (Perry Barr, Lab.). A man in the Derby district was injured in December, 1957. He periodically lost time from work. Eventually his doctor and his employer wrote to the medical superintendent of the hospital asking when the man could go for treatment. The man's doctor eventually received a reply from the consultant, in which the doctor's letter was described as "quite reasonable for you to write in this vein," and the firm's letter as "quite improper," and stating:

"Mr. (X) has a condition which is by no means an emergency and indeed has been provided with conservative treatment to ease the waiting period so that I consider there is no reason whatever why he should be advanced on the Health Service list. He was put on this list at the beginning of July so it is likely that his admission will be before Christmas."

The consultant went on to say:

"Since the matter is so urgent from an economic point of view, I would have thought he should consider having the job done privately, and he is in the happy position that, assuming he has a wife to look after him at home and that you would be prepared to look after him from time to time during the immediate post-operative period, he has a condition on which I would be prepared to operate privately as an out-patient under local anaesthetic, in which case he would incur only my operating fee of 20 guineas. I might point out that the N.H.S. out-patient operating waiting-list would involve a wait of some 12 to 18 months and the operation would be carried out by a junior, so that he is already as well off as he can be under the Health Service. It is possible that his firm would help him with his expenses."

Clearly, Mr. Howell commented, the consultant was saying that the man had to wait at least seven months for treatment, but that if he (the consultant) was paid 20 guineas he would treat the man at once. Secondly, and more important, he was saying that if he was not paid the money he would not do the operation at all. When the man eventually went into hospital he would receive inferior treatment under the Health Service and would not have the services of the consultant.

Finally, Mr. Howell criticized the merit award system. He understood that 279 consultants, which was 4% of the total, got the highest rate of £2,500; 698, or 10%, got the middle rate of £1,500; and 1,397, or 20%, got the lowest rate of £500. Nobody was ever told about this. It was causing considerable disturbance among consultants, who did not know which of their colleagues received the increase, and concern among the regional boards, who, although not having been consulted, had to find the money out of their own finances. It was an important principle that all those employed in any public service should not be paid in this secret manner.

Government Reply

Mr. RICHARD THOMPSON pointed out that the remuneration of consultants, with that of other medical staff, was under consideration by a Royal Commission, and that a working party had been set up jointly by the Ministry of Health and the medical profession to consider the structure of hospital medical staffing. Many of the problems raised by Mr. Howell would be dealt with in its report.

The preference of some consultants for a maximum part-time contract had been given statutory recognition since 1949 in the National Health Service (Amendment) Act. Applications for transfer from whole-time to part-time service were not automatically granted, and the statistics did not imply large-scale transfers. He agreed that the increase in hospital medical and dental officers employed whole-time had not been very great, and that part-timers had increased much more in proportion. Many of these, however, were new appointments into the Service, not transfers.

The Guillebaud Committee considered there was a valid case for a retention of part-time consultant appointments, but that the financial arrangements should not be such as would induce a consultant to seek a part-time rather than a whole-time appointment. That was also the Minister's view. Evidence on the differences in the bases of payment to part-time and whole-time consultants had been given to the Royal Commission. They must await any observations made in the Commission's report. A consultant's duties were set out in his contract with the regional board, whose responsibility it was to assess the amount of time required to perform them; and the Minister had more than once drawn attention to the importance of regular reviews of these assessments.

Pay-beds and Waiting-lists

The numbers of pay-beds set aside for private practice had not varied greatly. In 1949 the numbers were 6,647 in England and Wales and 729 in the Birmingham region. In 1953 the figures were 5,793 and 611; and in 1958 5,645 and again 611. In the same period the number of staffed beds provided without charge increased by 6,000. The number of pay-beds had thus gone down, and the number of non-paying beds had gone up.

It was true that it was often easier to obtain a bed quickly as a private patient, but it was by no means an invariable rule. In some of the larger teaching hospitals private patients had to wait longer. It would not be true to conclude that the abolition of private practice for hospitals would have an appreciable effect on the waiting-list. The number of private beds was little more than 1% of the total complement, and many of them were scattered over a large number of hospitals, perhaps with only two or four such beds. There was an express statutory reservation that nothing should prevent private accommodation being used for Health Service patients who urgently required it on medical grounds. In the Birmingham region in the past three years the average occupancy of pay-beds was 270 by paying patients and 130 by Health Service patients. They had therefore been making a considerable contribution.

The Government witness before the Royal Commission on remuneration had agreed that the system of merit awards had some disadvantages. On the other hand, the system, based on recommendations by the Spens Committee, had met the main requirements of securing higher remuneration on a basis of individual distinction rather than age or length of service, and the method had met broadly with acceptance. No superior alternative had yet been found, and the balance of advantage seemed to lie in the continuance of these arrangements.

On the complaint made by Mr. Howell, and the letter he read, the Parliamentary Secretary asked to be given full details.

MENTAL HEALTH BILL

The standing committee's work on the Mental Health Bill is near completion. At two meetings on April 14 and 16 the committee finished its work on the 146 clauses, and will have one further meeting to tidy up the schedules and consider a short selection of new proposals.

Review Tribunals' Procedure

In the miscellaneous matters grouped in Part IX are included the powers and procedure of the Mental Health Review Tribunals. Here, on Clause 122 (rules as to procedure), Dr. DONALD JOHNSON (Carlisle, Con.) moved

an amendment requiring that the rules, to be made by the Lord Chancellor, should include provision for the patient to be represented, to receive copies of all documents, and to have the right of examination and cross-examination. His purpose was to secure that the ordinary mental patient should be afforded the same protection as had been given to those who were brought into court.

Dr. EDITH SUMMERSKILL (Warrington, Lab.) also thought the point was worth examination. They had abolished the Board of Control, and should be careful to ensure that the safeguards of the review tribunals should operate as fairly as possible in the patient's interest.

The Minister of Health, Mr. D. WALKER-SMITH, pointed out that they were not dealing with the ordinary form of tribunal, still less a court of law. The amendment, based on the provisions of Clause 61, seemed to assume that all these proceedings would be formal hearings, as in a court of law (to which Clause 61 related). That would not necessarily be so. It was of the first importance that a formal hearing should be available if the patient or other applicant wanted it. It was also important that proceedings of this special character should not be imprisoned in the inescapable form of legal proceedings. Some of them would be informal procedures.

He envisaged a procedure broadly in accordance with that set out in para. 448 of the Royal Commission's report. He gave the committee these assurances: first, one member of the tribunal, and generally all of them, would see the patient; secondly, the patient could be represented before the tribunal; thirdly, the rules would be made by the Lord Chancellor, and referred in draft to the Council on Tribunals; fourthly, it was intended to apply the provisions of the Tribunals and Inquiries Act, 1958, to the review tribunals, so those safeguards would be available too. Finally, when a formal hearing was requested it would be granted, and then the proceedings would be in the hands of an experienced legal chairman, who could be relied on to make proper provision for all the requirements of what was compositely referred to as natural justice.

The amendment was withdrawn.

Censorship of Informal Patients' Letters

Clause 131 (correspondence of patients not subject to detention) brought up again the question of censorship. Mr. KENNETH ROBINSON (St. Pancras North, Lab.) complained that the clause gave the responsible medical officer or hospital authorities power to withhold both incoming and outgoing letters of informal patients, and in so doing in his view cut across the whole idea of informal treatment for mental disorder. Dr. EDITH SUMMERSKILL also advocated the deletion of the clause. Weighing the benefit to the community of the new approach to mental disease against the danger of an informal patient writing a letter of an obnoxious kind, she thought much of the good would be undone if it became known that there was a risk of a patient's letters being interfered with.

The MINISTER agreed that the question turned on a balance of considerations. It was a powerful argument that there should be no distinction between the informal mental patient and the ordinary general patient. On the other hand, although in general hospitals there would be general patients in some wards, and perhaps mental patients in psychiatric wards, there would also be, in the same psychiatric ward—literally side by side—detained patients and informal patients. Scrutiny of correspondence would apply to detained patients. Informal patients were suffering from the same mental disorders. They were subject to the same sensitivities in respect of incoming correspondence, and should in their own interests be protected from unsuitable letters. They were, many of them, subject to the same paranoic urges of sending out unsuitable correspondence, and the outside public should be protected.

They were embarking on an attempt to make the informal procedure the general pattern. Nothing should be done which would jeopardize it. If there should be a stream of letters from informal patients causing offence they would be accused of having gone too far, and told that they must have regard for the outside community by having more Part IV patients and fewer informal patients. If this clause were omitted, nothing could be done about the correspondence of paranoic informal patients except to make them compulsory patients. For all these reasons he thought the balance came down on the side for Mr. Robinson and Dr. Summerskill.

Dr. A. D. D. BROUGHTON (Batley and Morley, Lab.), having seen some of the letters that mental patients could write, also came down in favour of retaining the clause.

After some further discussion an amendment to delete the clause was withdrawn and the clause agreed to.

QUESTIONS IN THE COMMONS

Law on Suicide

Mr. KENNETH ROBINSON asked the Home Secretary on April 16 for a statement on his meeting with the Joint Committee of the British Medical Association and the Magistrates' Association on the law of suicide, and if he had any decision to announce on amending legislation. Mr. R. A. BUTLER stated that a helpful meeting between officials of the Home Office and of the Ministry of Health and representatives of the Joint Committee of the British Medical Association and the Magistrates' Association took place last month. The meeting explored the crucial problem of ensuring that persons who attempted to commit suicide received treatment for their mental, as well as their physical, condition. The existing law did ensure this, although he recognized that it had unsatisfactory features, and before they changed it he wanted to be satisfied that there were workable alternatives. He was not in a position to say when it would be possible to legislate.

Prison Medical Officers' Rents

Mr. B. JANNER (Leicester, North-West, Lab.) asked if the Home Secretary was aware that about 150 prison medical officers occupying Government-owned houses were having their rents put up under the provisions of the Rent Act, 1957, to two or three times the original amount, and what he proposed by way of compensation.

Mr. BUTLER said that the increase proposed affected 93 prison medical officers. It arose from the general decision that rents for Government-owned quarters should be related as closely as possible to those charged by private landlords. The matter was under discussion with the staff association concerned.

Report on Cost of Prescribing

Mr. JAMES LINDSAY (Devon, North, Con.) asked the Minister of Health on April 20 whether he had yet received the report of the Committee on the Cost of Prescribing; and what action he was proposing to take upon it.

Mr. D. WALKER-SMITH: Yes, I am considering the recommendations in the report, which will be published on or about May 12. Mr. LINDSAY asked if the Minister would consult the British Medical Association and other interested bodies; when were conclusions likely to be reached on the recommendations; and how far had those in the interim report been implemented. Mr. WALKER-SMITH said that the interim recommendations had been or were in process of being implemented. He was proposing to consult the B.M.A. and other interested organizations as soon as the final report had been published. Action on the recommendations would be taken as soon as possible in the light of those consultations.

Prescription Charges

Mr. A. BLENKINSOP (Newcastle upon Tyne, East, Lab.) asked the Minister what recent representations he had received from the B.M.A. reaffirming their opposition to prescription charges, and urging their abolition on the grounds of economy and the avoidance of hardship; and what reply he had sent. Mr. WALKER-SMITH said that a

resolution passed in July of last year by the Representative Body of the B.M.A. was brought to his attention. He had undertaken to bear the Association's views in mind.

Influenza and Chest Diseases

The Minister of Health provided Mr. SOMERVILLE HASTINGS (Barking, Lab.) with the following information on death rates per million population from chest diseases (influenza, bronchitis, and pneumonia) in each of the first three months of this year, compared with 1958:

	London Administrative County		England and Wales	
	1958	1959	1958	1959
January	4,669	3,078	3,124	2,214
February	3,254	8,695	2,466	4,721
March	2,377	3,961	1,880	3,684

These are provisional figures based on registrations of deaths as reported weekly to the Registrar-General.

Tuberculosis Among Women

Mrs. HARRIET SLATER (Stoke-on-Trent, North, Lab.) asked what was the incidence rate of tuberculosis among women in the child-bearing age group of 18 to 40 years. Mr. WALKER-SMITH replied that exact information in this form was not available. The notification rate of tuberculosis in 1957, the latest year for which full information was available, among women aged from 20 to 44 years inclusive, was 95.4 per 100,000.

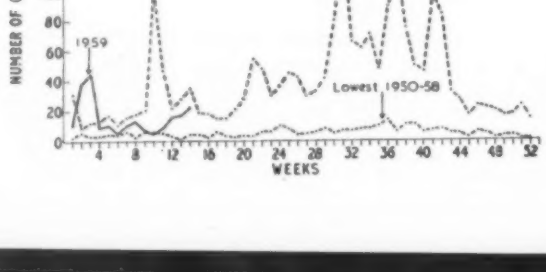
Letter-box Psychology

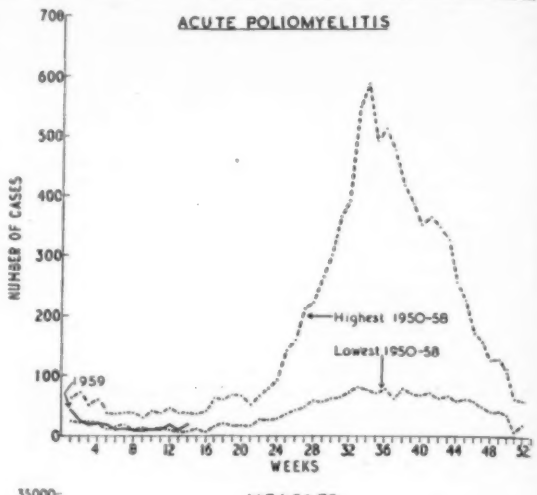
Mr. D. MARSHALL (Bodmin, Con.) asked the Postmaster-General on April 8 what progress was being made with his proposal that the public should use codes in order to facilitate the mechanization of letter sorting. Mr. E. MARPLES stated that good progress was being made. A survey of public opinion aimed at finding out how far people would be prepared to use postal codes was well advanced. First indications were that the response would be favourable. The Applied Psychology Research Unit of the Medical Research Council at Cambridge was helping them to find the best kind of code. Meantime they were pressing on with the design of machinery for coding and automatic sorting of letters.

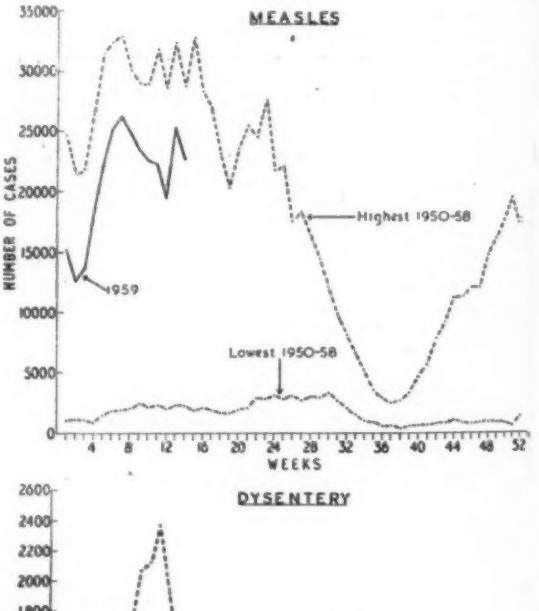
Vital Statistics

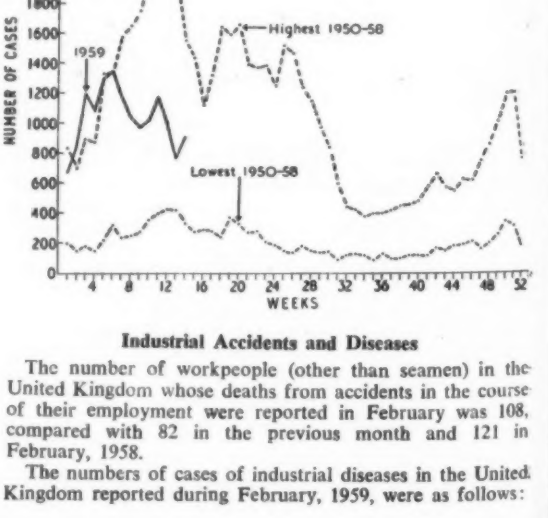
Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the years 1950–8 are shown thus ------, the figures for 1959 thus ———. Except for the curves showing notifications in 1959, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.









Industrial Accidents and Diseases

The number of workpeople (other than seamen) in the United Kingdom whose deaths from accidents in the course of their employment were reported in February was 108, compared with 82 in the previous month and 121 in February, 1958.

The numbers of cases of industrial diseases in the United Kingdom reported during February, 1959, were as follows:

Lead poisoning 6, aniline poisoning 1, epitheliomatous ulceration 17, chrome ulceration 11; total 35. There were no deaths.—*Ministry of Labour Gazette*, March, 1959.

Week Ending April 11

Infectious Diseases

Areas where numbers of notifications were high in the latest two weeks for which figures are available.

	Week Ending April 4	Week Ending April 11
Measles		
Cambridge	104	187
Cambridge M.B.	67	135
Devonshire	339	390
Plymouth C.B.	206	184
Essex	2,066	1,784
Wesh Ham C.B.	159	175
Basildon U.D.	125	237
Gloucestershire	447	595
Bristol C.B.	193	232
Kent	1,322	1,125
Orpington U.D.	178	188
Lancashire	1,881	1,855
Liverpool C.B.	188	157
Manchester C.B.	332	319
St. Helens C.B.	150	115
London	1,388	1,376
Lambeth	129	117
Lewisham	138	148
Wandsworth	151	160
Northumberland	802	865
Newcastle upon Tyne C.B.	340	419
Surrey	1,697	1,428
Croydon C.B.	240	313
Warwickshire	1,438	1,144
Birmingham C.B.	725	732
Yorkshire West Riding	2,574	2,488
Bradford C.B.	212	156
Leeds C.B.	551	552
Sheffield C.B.	288	257
Glamorganshire	495	450
Cardiff C.B.	232	210
Dysentery		
Lancashire	121	139
Blackburn C.B.	21	62
Lincolnshire	69	51
Grimsby C.B.	40	26
London	82	122
Greenwich	10	13
Hampstead	1	29
Lambeth	4	14
Southwark	3	10
Warwickshire	63	78
Birmingham C.B.	21	34
Coventry C.B.	37	38
Worcestershire	18	81
Evesham R.D.	3	70
Yorkshire West Riding	81	80
Bradford C.B.	19	19
Leeds C.B.	33	32
Glamorganshire	43	38
Cardiff C.B.	23	15
Paratyphoid Fever		
London	2	13
Southwark	0	10
Food-poisoning		
Warwickshire	3	152
Birmingham C.B.	0	149
Acute Pollomyelitis		
Warwickshire, Birmingham C.B.	0	3

INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **April 4** (No. 13) and corresponding week 1958.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the whole of England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES	1959 Eng. & Wales	1959 Lond.	1959 Scot.	1959 N. Ire.	1959 Eire	1958 Eng. & Wales	1958 Lond.	1958 Scot.	1958 N. Ire.	1958 Eire
Diphtheria	2	1	3	0		2	0	2	0	1
Dysentery	771	82	180	11	3	1,586	110	248	7	7
Encephalitis, acute	4	1		0		1	0		0	
Enteric fever:										
Typhoid	0	0	0	0	1	3	0	1	1	
Paratyphoid	17	2	3(B)	0		4	0	0	0	3(B)
Food-poisoning	117	13	0	1		154	19	20	0	
Infective enteritis or diarrhoea under 2 years				2	23				10	24
Measles*	25,266	1388	936	470	360	4,289	165	105	23	16
Meningococcal infection	28	0	14	0	2	22	5	11	2	1
Ophthalmia neonatorum	18	2	6	0		36	1	2	0	
Pneumonia†	761	38	319	45	26	621	49	322	27	2
Poliomyelitis, acute:										
Paralytic	6	0	1	1	1	17	0	0	0	3
Non-paralytic	3	0	1			4	0			
Puerperal fever§	249	35	13	1		223	50	8	2	1
Scarlet fever	916	56	60	21	16	982	67	86	23	18
Tuberculosis:										
Respiratory	589	68	62	13		545	73	148	24	
Non-respiratory	46	4	10	1		73	4	17	3	
Whooping-cough	608	27	44	37	108	651	27	40	2	29

DEATHS	1959 Eng. & Wales	1959 Lond.	1959 Scot.	1959 N. Ire.	1959 Eire	1958 Eng. & Wales	1958 Lond.	1958 Scot.	1958 N. Ire.	1958 Eire
Diphtheria	0	0	0	0	0	0	0	0	0	0
Dysentery	2	0		0		2	0		0	
Encephalitis, acute		0		0	0		0			0
Enteric fever	0	0	0			0	0	0	0	
Infective enteritis or diarrhoea under 2 years	3	0	0	0	0	9	0	0	0	0
Influenza	294	7	7	11	12	71	2	3	0	0
Measles		0	0	0	1		0	0	0	0
Meningococcal infection		0	0				0	0		
Pneumonia	818	57	39	30	30	838	72	48	17	15
Poliomyelitis, acute	0	0		0	0	1	0		0	0
Scarlet fever		0	0	0	0		1	0	0	0
Tuberculosis:										
Respiratory	105	9	5	0	6	109	12	10	0	3
Non-respiratory		0	1	0	0		2	0	0	0
Whooping-cough	1	0	0	0	0	0	0	0	0	0
Deaths 0–1 year	338	35	41	12	17	344	44	35	2	24
Deaths (excluding stillbirths)	11,573	838	666	188	251	12,732	1022	744	152	211
LIVE BIRTHS	16,283	1317	1184	236	307	15,582	1303	1052	272	446
STILLBIRTHS	362	25	20			291	20	30		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Medical News

Royal Free Chair of Medicine.—Dr. SHEILA SHERLOCK, lecturer in medicine at the Postgraduate Medical School of London, has been appointed to the University Chair of Medicine tenable at the Royal Free Hospital School of Medicine.

Dr. Sherlock graduated M.B. with honours at Edinburgh University in 1941, and was awarded the Ettles Scholarship for the most distinguished bachelor of medicine and surgery of the year. She obtained the M.R.C.P. in 1943, and her M.D. with gold medal in 1945. After a period as assistant in the department of surgery at the University of Edinburgh under Sir James Learmonth, she took a research post at the Postgraduate Medical School of London and in 1944 was awarded a Beit Memorial Research Fellowship. In 1947 she was awarded a Rockefeller Travelling Fellowship which she held at Yale University. Dr. Sherlock is known especially for her work on diseases of the liver, and is the author of a monograph on the subject.

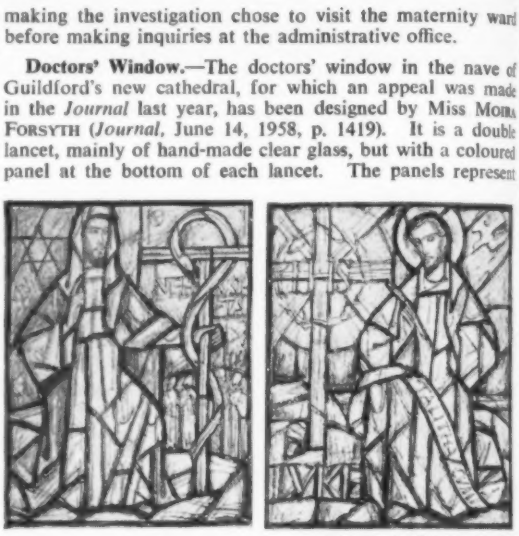
British Heart Surgeons for Moscow.—Mr. W. P. CLELAND, Dr. D. G. MELROSE, Mr. H. H. BENTALL, and four other members of their Postgraduate Medical School (Hammersmith Hospital) Cardiac Surgery Team left for Moscow on April 23 for a series of demonstrations of the clinical use of the Melrose heart/lung machine and the technique of elective cessation of the heart (both British developments), as well as British methods of open intracardiac surgery. This operative work will be undertaken by invitation of Professor BAKULEV, President of the Academy of Medical Sciences of the U.S.S.R. in the Institute of Thoracic Surgery.

During their stay in Moscow they will be the guests of the Soviet Government. The transport expenses of personnel and equipment are being defrayed by grants from the British Council, the Nuffield Foundation (who have been mainly responsible for the expenses of developing the heart/lung machine in this country), the Postgraduate Medical School of London, the Boards of Governors of Hammersmith, and of King's College and of the Brompton hospitals. A Melrose machine has been purchased by the Russian Government for use in Moscow, and this is the machine which will be employed during the demonstrations. Transport facilities have been assisted by New Electronic Products Ltd. (who collaborated in solving engineering problems in relation to the machine and who now build the market product). Anaesthetic equipment and anaesthetic drugs have been made available to the team by Charles King Ltd., Medical Industrial Equipment Ltd., and Imperial Chemical Industries Ltd.; oxygen equipment has been furnished by Oxygenaire; suture materials by Ethicon Sutures Ltd.; and instruments for use in the demonstration operations by the Genito-Urinary Co. Ltd.

Mr. CLELAND, the chief cardiac surgeon of the team, will be the bearer of a presentation set of textbooks and monographs of thoracic surgery to deliver as a gift to their Russian colleagues from the firm of H. K. Lewis Ltd. The team expect to spend two or three weeks in Moscow, and some eight or ten operations have been planned.

Complaint to Press Council.—At the quarterly meeting of the General Council of the Press in London on April 14, presided over by Sir Linton Andrews, the Marquess of Normanby, as Chairman of King's College Hospital, complained about a report which appeared in the *Sunday Pictorial* on January 11 under the heading "4-Hour Baby sent out of Hospital." He declared that the report suggested lack of proper care of the patient by the hospital, and that two reporters had obtained access to the maternity ward by trespass. Evidence submitted by the paper showed that in the first instance the complaint had been made to it by the baby's father. The Press Council considered that the complaint made to the *Sunday Pictorial* by the father was of public interest and the editor was entitled to publish it, especially as the newspaper gave prominence at the same time to the hospital's statement on the matter and its assurance that the health of the mother and the baby was not endangered by the early discharge from the maternity ward. It was unfortunate, however, that the reporters making the investigation chose to visit the maternity ward before making inquiries at the administrative office.

Doctors' Window.—The doctors' window in the nave of Guildford's new cathedral, for which an appeal was made in the *Journal* last year, has been designed by Miss MOIRA FORSYTH (*Journal*, June 14, 1958, p. 1419). It is a double lancet, mainly of hand-made clear glass, but with a coloured panel at the bottom of each lancet. The panels represent



[Thomas A. Wilkie, Guildford

Moses setting up the serpent of brass upon a standard, and the raising of Jairus's daughter. Donations for the window have already reached £800, more than half the amount that is needed. Further contributions should be sent to Dr. F. A. BELAM, 1, Westfield, Epsom Road, Guildford, Surrey.

Wellcome Foundation.—On May 1 Sir HENRY DALE, O.M., F.R.S., chairman of the Wellcome Trust, will declare open the first two completed stages of the five-year development plan of the Wellcome Research Laboratories, Beckenham. One of the new buildings is for the production of poliomyelitis vaccine, two are for virus work, and one for anaerobic bacteriology. This major development programme was begun in 1955 to provide up-to-date facilities for the Foundation's work in the field of research and the production of biological products. It is being carried through in three stages and will cost over £2m.

University Nursing Training.—In June the department of social and preventive medicine at Manchester University is to start an experimental four-year course in community nursing and health visiting. Successful students will qualify for State registration on the General Nursing Council's register and for a university diploma.

Central Middlesex Hospital.—The new diet kitchen, hospital shop, and central sterile service building at the hospital were officially handed over by Lord COTTESLOE, chairman of the North-west Metropolitan Regional Hospital Board, on April 21.

Chest Diseases.—On April 21 Dr. HORACE JOULES, medical director of the Central Middlesex Hospital, described last winter as the worst he could remember from a medical point of view, and urged that a Royal Commission be appointed to inquire into the rapidly growing problem of chest diseases.

British Cardiac Society.—The 38th annual general meeting of the British Cardiac Society was held at Cardiff on April 9 under the chairmanship of Dr. WILLIAM PHILLIPS.

Pakistan Donation.—The government of Pakistan has made a donation of £1,000 to the Building Extension Appeal Fund of the Postgraduate Medical School of London University. Since 1947 over 200 medical students from Pakistan have been trained at the School.

University of Sydney.—Dr. N. MALLESON, physician-in-charge of the Student Health Service, University College, University of London, has been appointed the first director of the recently established Student Health Service at the University of Sydney.

COMING EVENTS

Third Almroth Wright Lecture.—"Studies on Bacterial Infections of the Kidney," by Professor PAUL B. BEESON. For details see advertisement p. 55 of this week's *Journal*.

National Society for Mentally Handicapped Children.—The Annual Convention will be held at Church House (Assembly Hall), Dean's Yard, Westminster, London, S.W.1, on April 25 at 2.30 p.m. Further details from the General Secretary, N.S.M.H.C., Kingsway Chambers, 162a, The Strand, London, W.C.2.

Faculty of Anaesthetists, R.C.S. (Eng.).—A scientific meeting on "The Neuromuscular Junction" will be held on May 2. Details from the Secretary of the Faculty, Royal College of Surgeons, Lincoln's Inn Fields, London, W.C.2.

United Hospitals Choir.—A concert will be given in aid of the Imperial Cancer Fund at the Chelsea Town Hall on May 5 at 8 p.m. Details from the Secretary, 18, West Side, Clapham Common, London, S.W.4.

Society for Psychosomatic Research.—A study group on the psychosomatic aspects of paediatrics will be held on May 8, 9, and 10 at the Royal College of Physicians, Pall Mall East, London, S.W.1. Details from Dr. D. O'NEILL, 130, Harley Street, London, W.1.

Faculty of Radiologists.—The third Knox Memorial Lecture on "Medicine, Radiology, and the Law" will be delivered by Dr. S. COCHRANE SHANKS at the Royal College of Surgeons of England, Lincoln's Inn Fields, London, W.C.2, at 4.30 p.m. on May 8.

Royal Medico-Psychological Association.—The Spring Quarterly Meeting will be held at Newcastle upon Tyne on May 6 and 7. Open to members and their guests. Details from the Secretary, R.M.P.A., 11, Chandos Street, Cavendish Square, London, W.1.

NEW ISSUES

The journals listed below are obtainable from the Publishing Manager, B.M.A. House, Tavistock Square, London, W.C.1.

British Journal of Ophthalmology.—Issued monthly (£6 annually). The new issue (Vol. 43, No. 4) includes:

INTRACAPSULAR CATARACT EXTRACTION USING ALPHA-CHYMO-TRYPSIN. J. E. H. Cogan, H. M. Symons, and D. C. Gibbs.
CATARACT EXTRACTION WITH THE AID OF ALPHA-CHYMO-TRYPSIN. D. Ainslie.
ALPHA-CHYMO-TRYPSIN IN CATARACT EXTRACTION. E. C. Zorab.
SUDDEN BLINDNESS IN CRANIAL ARTERITIS. G. Parsons-Smith.
DIKTYOMA. B. S. Cardell and M. J. Starbuck.
SEESAW NYSTAGMUS. O. A. Jensen.
OPERATION ON VERTICAL MUSCLES IN CASES OF NYSTAGMUS. D. Pierse.
INFLUENCE OF PROTEIN DEFICIENCY AND SEX ON THE DEVELOPMENT OF OCULAR LESIONS AND SURVIVAL TIME OF THE VITAMIN A-DEFICIENT RAT. D. S. McLaren.
TUBADIL IN OPHTHALMIC SURGERY—ITS EFFECT ON INTRA-OCULAR PRESSURE. R. Bryce-Smith and F. K. Boston.
MALIGNANT LYMPHATIC TUMOURS OF THE ORBIT—A REVIEW OF EIGHT CASES. V. H. Smith.
MARFAN'S SYNDROME. Doris Rose.

Abstracts of World Medicine.—Issued in the first week of each month, this journal contains abstracts of important papers selected from the current medical literature of the world. Annual subscription £4 4s.

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Saturday, April 25

NORTH-EAST METROPOLITAN THORACIC SOCIETY.—At St. Ann's Hospital, Tottenham, N., 10 a.m., general meeting. Scientific papers.

Monday, April 27

●HUNTERIAN SOCIETY.—At Talbot Restaurant, London Wall, E.C., 7 for 7.30 p.m., dinner meeting. 8.30 p.m., annual general meeting. Address by Mr. Peter Wilson: London as the Centre of the Art Market of the World.
MANCHESTER MEDICAL SOCIETY: (1) SECTION OF ODONTOLOGY.—At Lecture Room, Dental Hospital, 4.30 for 5 p.m., Dr. J. Blair Hartley: Radiation Hazards in Dental Radiology. (2) SECTION OF GENERAL PRACTICE.—At Large Anatomy Theatre, Manchester University Medical School, 8.30 for 9 p.m., Dr. H. T. Howat and Mr. A. Nicholson: Management of Obstructive Jaundice.
POSTGRADUATE MEDICAL SCHOOL OF LONDON.—4 p.m., Sir Russell Brain: Consciousness and Unconsciousness.

Tuesday, April 28

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. N. R. Mackay: Applied Physics (2).
LONDON UNIVERSITY.—At Institute of Obstetrics and Gynaecology, 2 p.m., special university lecture in medicine by Professor J. P. Greenhill (Chicago): Recent Progress in Obstetrics and Gynaecology.
ROYAL COLLEGE OF SURGEONS OF ENGLAND.—3.45 p.m., Arnott Demonstration by Miss J. Dobson: John Hunter's Museum.
ROYAL STATISTICAL SOCIETY: MEDICAL SECTION.—At Small Lecture Theatre, London School of Hygiene and Tropical Medicine, 5.30 p.m., discussion: Matched Pairs. To be opened by Dr. Ian Sutherland, Mr. L. T. Wilkins, and Dr. A. N. Oppenheim.
ST. MARY'S HOSPITAL MEDICAL SCHOOL.—At Wright-Fleming Theatre, 5 p.m., Mr. G. W. Theobald: Induction of Labour in Perspective.
WEST END HOSPITAL FOR NEUROLOGY AND NEUROSURGERY.—5.30 p.m., Dr. T. Rowland Hill: Neurology.

Wednesday, April 29

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. R. W. Riddell: Invasion of Keratin by Fungi *in vitro* and *in vivo*.
INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Dr. J. Smart: Pulmonary Physiology and its Applicability to the Treatment of Chest Conditions.
MANCHESTER MEDICAL SOCIETY: (1) SECTION OF MEDICINE.—At Clinical Sciences Building, York Place, 4.30 for 5 p.m., clinical meeting. Demonstration by Dr. J. F. Wilkinson and members of the Department of Haematology. (2) SECTION OF PATHOLOGY.—4.30 for 5 p.m., Laboratory Meeting of Departments of Pathology and Bacteriology, York Place.
POSTGRADUATE MEDICAL SCHOOL OF LONDON.—2 p.m., Dr. R. E. O. Williams: Epidemiology of Streptococcal Infections.
ROYAL COLLEGE OF SURGEONS OF ENGLAND AND INSTITUTE OF UROLOGY.—At the College, 5 p.m., Urology Lecture by Mr. J. D. Fergusson: Cysts of the Kidney
ROYAL INSTITUTE OF PUBLIC HEALTH AND HYGIENE.—3.30 p.m., Mr. H. R. Duffield-Harding: Some Aspects of Hygiene in Relation to the Production and Service of Clean Food (illustrated).

Thursday, April 30

HONEYMAN GILLESPIE LECTURE.—At Anatomy Theatre, University New Buildings, Edinburgh, 5 p.m., Sir Eric Riches: The Ureter.
INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. G. A. G. Peterkin: Rare Drug Rashes.
LONDON UNIVERSITY.—At King's College, Strand, W.C., 5.30 p.m., special university lecture in pharmacology by Professor Walter Modell (U.S.A.): Problems in the Evaluation of Drugs in Man.
POSTGRADUATE MEDICAL SCHOOL OF LONDON.—4 p.m., Professor G. M. Bull: Regulation of Body Water.
ROYAL COLLEGE OF SURGEONS OF ENGLAND AND INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—At the College, 5.30 p.m., Otolaryngology Lecture by Professor M. A. Rushton: Cystic Conditions of the Upper Jaw.
ROYAL EYE HOSPITAL.—5.30 p.m., Dr. T. H. Whittington: Aspects of Refraction Work—(3) Hypermetropia and Myopia Compared.
ROYAL NORTHERN HOSPITAL.—2.45 p.m., Mr. Patrick Clarkson: Open Injuries of the Hand (with film).

Friday, May 1

●INSTITUTE OF DERMATOLOGY.—5.30 p.m., clinical demonstration by Dr. S. L. Gold
INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Mr. N. R. Barrett: clinical demonstration.
POSTGRADUATE MEDICAL SCHOOL OF LONDON.—10 a.m., Mr. F. N. Glover: Surgery of Parathyroid Disease.

Saturday, May 2

INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—11.30 a.m., Professor Andre Djourno (Paris): Acoustic Stimulation of Nerve Fibres.

Sunday, May 3

INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—10.15 a.m. to 12.30 p.m., Seminar for general practitioners. Common E.N.T. conditions by staff of Professorial Unit.
UNIVERSITY COLLEGE HOSPITAL.—10.15 a.m., meeting in Front Hall of main hospital. Lecture-demonstration for general practitioners. Clinical demonstration by Professor M. L. Rosenheim: Nephritis.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Mackie.—On April 14, 1959, at Military Families Hospital, Chatham, Kent, to Barbara, wife of Captain John Mackie, R.A.M.C., a sister for Robin—Fiona.

DEATHS

Alexander.—On April 5, 1959, George John Alexander, M.B., B.Ch., of Lancaster, aged 68.
Heath.—On April 3, 1959, at Fleet Hospital, Philip Maynard Heath, M.S., F.R.C.S., of Fleet, Hants, aged 82.
Key.—On March 28, 1959, the result of an accident, Eileen Mary Key, M.B., Ch.B., of 12, Millcross Road, Portslade, Sussex, aged 41.
McFarlane.—On March 30, 1959, James McFarlane, L.R.C.P.&S.Ed., L.R.F.P.S., L.D.S., of 29, Church Road, Tunbridge Wells, Kent.
Moncrieff.—On April 2, 1959, at R.N. Hospital, Plymouth, Devon, Leonard Alexander Moncrieff, M.B., Ch.B., Surgeon Captain, R.N., retired, of Culfargie, Kingsbridge, Devon.
Mowat.—On April 3, 1959, in a nursing-home, Stirling, Janet Craig Mowat, M.B., Ch.B., of Callander, Perthshire.
Murrell.—On April 1, 1959, at the Royal Sussex County Hospital, Ernest Bartram Murrell, M.B., B.Chir., D.Obst.R.C.O.G., D.A., of 10, Varndean Gardens, Brighton, Sussex, late of Malaya, aged 60.
Renwick.—On March 28, 1959, in hospital, Gordon Alick Renwick, M.B., Ch.M., of Riverdale, Prestbury, Cheshire, aged 70.
Richmond.—On March 30, 1959, at Stoke-on-Trent, Staffs, Thomas Heyliger Richmond, O.B.E., T.D., M.B., F.R.C.S.Ed., aged 79.
Sablin.—On March 29, 1959, at the Red House, Stoke-by-Clare, Suffolk, Nikolai Sergeevich Sablin, M.R.C.S., L.R.C.P., late of Stepney Green, London, E.
Savage.—On March 30, 1959, at 53, Victoria Road, Acocks Green, Birmingham, Warwicks, Horace Simkin Savage, M.D., formerly of 33, Highfield Road, Alum Rock, Saltley, Birmingham.
Verity.—On March 24, 1959, Robert James Stanley Verity, L.M.S.S.A., of Garndiffaith, Pontypool, Mon, aged 89.

Any Questions?

We publish below a selection of those questions and answers which seem of general interest. It is regretted that it is not possible to supply answers to all questions submitted.

Treatment for Pemphigus

Q.—*Is there any effective treatment for pemphigus? Is it worth trying the newer steroids?*

A.—It is presumed that the questioner refers to pemphigus vulgaris, which is a very distressing condition of obscure origin. It used to be regarded as invariably fatal, but often the eruption can be controlled by corticosteroids. Large doses of A.C.T.H. and cortisone may have to be given together, and in America doses exceeding 1 g. a day were found necessary in some cases. We have usually controlled our patients on doses of A.C.T.H. ranging from 100 to 300 mg. a day, with cortisone up to the same level, but it may well be that some of the newer corticosteroids would be effective at a lower dosage. It is well to give high doses at first to control the eruption, and then rapid reduction may be made to find the minimum maintenance dose. Once found, this may have to be continued for several years, hoping that the disease, if controlled, will eventually clear up. Some patients have been reported as remaining free from symptoms for periods as long as five years.

If the patient is elderly, the condition which clinically resembles pemphigus vulgaris, and is called pemphigoid, has a better prognosis and is regarded by many as a variation of dermatitis herpetiformis. It would be well to have a dermatological opinion on any case before starting treatment.

Small-pool Plasma

Q.—*What is the present view on the infusion of small-pool plasma? Do the proteins reduce the negative nitrogen balance which follows surgery on acutely ill patients?*

A.—The use of small-pool plasma has declined. So far as the purpose was to reduce the incidence of serum hepatitis it is no longer necessary, since storage of plasma at room temperature for at least six months appears to kill any virus present in the plasma.

The negative nitrogen balance which follows major operations on acutely ill or any other kind of patient may be resolved into two components. One of these is due to starvation, which may vary widely in degree and duration from one clinic to another and may be increased by the occurrence of post-operative complications. The other component seems to be due to a tissue katabolism which is inseparably related in some way to the infliction of severe injury and is probably brought about by changes in the secretory activity of the pituitary and adrenal glands. Of these two components, only the first can be affected therapeutically by the prevention of starvation, and there is no doubt that this is best done by resuming at as early a stage as possible the consumption of a good mixed diet. The fate in the body of injected or ingested protein of any kind is governed by certain nutritional principles. In the present connexion the most important of these is that at any time, unless there is a coincident supply of sufficient non-protein calories to satisfy the current energy requirements of the body, part or the whole of the protein will be deaminated and the resulting non-protein carbohydrate residues used to provide calories. If after operation it is desired to mitigate or prevent protein starvation by the intravenous infusion of human plasma as a source of protein, it is essential to provide as well at least 1,800 calories per 24 hours from other sources. Until recently this could not be achieved by the infusion of glucose solutions during the early post-operative period without the risk of overloading the body with water. The addition of fructose or alcohol increased the caloric content of the solution, but only the recent development of a stable commercial fat emulsion has made the provision of adequate calories readily feasible: a 15% fat emulsion supplies 1,200 calories per litre. Homologous plasma protein has been shown to be nutritionally adequate, and, provided adequate non-protein calories are supplied in addition, human plasma is a good but expensive source of protein.

Masks in Nursing the Newborn

Q.—*Should nurses wear masks when attending newborn babies?*

A.—This is a controversial question and the practice varies widely. Duguid and Wallace[1] have shown that direct droplet infection is not the most important mode of transmission of organisms, although a high percentage of hospital staff and newborn infants may become nasal carriers of staphylococci.[2,3] In a carefully controlled experiment Forfar and Maccabe[4] have shown that gowning and masking produced no significant reduction in staphylococcal infection in the newborn and have pointed out that expense, time consumption, and problems of administration are not justified by results.

To be effective, a mask should be impermeable to large and small droplets, preferably muslin interleaved with "cellophane." It is doubtful whether any mask worn with reasonable comfort can be relied on to prevent transmission of organisms. A mask must also be worn correctly—for a limited period and not handled or removed and replaced. The damage done in such circumstances is comparable to the shaking of an infected handkerchief.[5] However, newborn babies are susceptible to organisms other than staphylococci, and, while attendants suffering from coryza and influenza should be excluded from their vicinity, masking of attendants would probably reduce the risk of cross-infection during the incubation period.

Masking is not, then, the most important measure for protection of infants against infection. Hand washing, minimal handling, the use of skin antiseptics such as chlorhexidine, and the exclusion of attendants with respiratory or skin sepsis are of greater importance.

REFERENCES

1. Duguid, J. P., and Wallace, A. T., *Lancet*, 1948, **2**, 845.
2. Barber, M., *Proc. roy. Soc. Med.*, 1956, **49**, 633.
3. Cook, J., Parish, J. A. and Shooter, R. A., *Brit. med. J.*, 1958, **1**, 74.
4. Forfar, J. O., and Maccabe, A. F., ibid., 1958, **1**, 76.
5. Andrewes, C. H., *Lancet*, 1940, **2**, 770.

Collected Articles from the "British Medical Journal"

The following books are available through booksellers or from the Publishing Manager, B.M.A. House. Prices, which include postage, are now the same for both inland and overseas.

Emergencies in General Practice (26s. 9d.).

Refresher Course for General Practitioners, Volumes 2 and 3 (26s. 9d. each).

Clinical Pathology in General Practice (22s. 3d.).

Any Questions?, Volumes 2 and 3 (8s. 3d. each).

All communications with regard to editorial business should be addressed to THE EDITOR, BRITISH MEDICAL JOURNAL, B.M.A. HOUSE, TAVISTOCK SQUARE, LONDON, W.C.1. TELEPHONE: EUSTON 4499. TELEGRAMS: *Aitiology, Westcent, London.* ORIGINAL ARTICLES AND LETTERS forwarded for publication are understood to be offered to the *British Medical Journal* alone unless the contrary be stated.

Authors desiring REPRINTS should communicate with the Publishing Manager, B.M.A. House, Tavistock Square, W.C.1, on receipt of proofs. Authors overseas should indicate on MSS. if reprints are required, as proofs are not sent abroad.

ADVERTISEMENTS should be addressed to the Advertisement Director, B.M.A. House, Tavistock Square, London, W.C.1 (hours 9 a.m. to 5 p.m.). TELEPHONE: EUSTON 4499. TELEGRAMS: *Britmedads, Westcent, London.*

MEMBERS' SUBSCRIPTIONS should be sent to the SECRETARY of the Association. TELEPHONE: EUSTON 4499. TELEGRAMS: *Medisecra, Westcent, London.*

B.M.A. SCOTTISH OFFICE: 7, Drumsheugh Gardens, Edinburgh.